THE MECHANICS OF THE
DIGESTIVE TRACT

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BY

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THESE PAGES ARE

AFFECTIONATELY DEDICATED

TO

MY FATHER AND MOTHER

PREFACE

In 1913, while doing some work on the absorption of gases injected into loops of intestine, I noticed differences in irritability in different parts of the bowel; that is, the jejunum reacted actively to distention, while the ileum generally responded but little. It promptly occurred to me that this graded difference in irritability might account for the downward progress of food in the bowel, because it seemed reasonable to suppose that material would have to move from the more irritable and active regions to the less irritable and active ones. While attempting to show these differences in irritability with excised segments of intestine, I found that the rate of rhythmic contraction of the muscle is graded downwards from the pylorus to the ileocecal sphincter. Remembering how much the heart specialist has profited by the careful study of conduction along a similar rhythmic gradient from the sinus node to the ventricle, I was filled with the hope that a careful analysis of the gradient found in the bowel might throw light on the mechanism of peristalsis and might put more system into the science of gastro-enterology.

As time goes on that hope seems more and more likely to be realized. During 1915, gradients of rhythmicity, irritability and latent period were found in the stomach; and a sort of pacemaker was located on the lesser curvature near the cardia. Later, my assistants and I showed that in addition to the rhythmic gradients in the stomach and intestine, and probably underlying them, there are gradients in metabolism. Ways were found in which these chemical gradients can theoretically be upset; and actually they were found upset in many of the sickly or distempered animals studied.

While this laboratory work was going forward, a careful review was made of our knowledge of peristalsis both in health and disease; and it was found that the idea of a gradient of forces which can be flattened or reversed offers the best, the simplest, and often the only explanation for many of the phenomena observed by the physiologist, the internist, the roentgenologist and the surgeon.

In 1920, at the kind invitation of Dr. J. T. Case, then President of the American Roentgen Ray Society, I prepared a short summary of my views which was presented before the Society's meeting in Minneapolis as the First Caldwell Lecture. This little book has developed as an elaboration and amplification of that lecture. I only hope it will be a help and convenience to those practitioners and roentgenologists who are already finding the gradient theory useful in their work, and who wish to know more about the subject. I have tried to make it sufficiently technical for the research worker in physiology and yet sufficiently readable and practical for the medical student or the physician who is looking for help on a clinical or surgical problem. Such students and practitioners will find summed up in Chapters IV, VIII, IX, X and XI most of the data essential to an understanding of the mechanics of digestion; and with the help of the extensive bibliography and the paragraphs at the end of Chapter XII, they can easily gain access to everything else of value which has been written on the subject. I think the chapter on technic will be helpful to research workers, because the information embodied in it has hitherto been scattered through many articles in different languages.

Although many of the observations upon which the idea rests have been verified repeatedly, and although, as Wallace says, "there is no more convincing proof of the truth of a comprehensive theory than its power of absorbing and find-

ing a place for new facts, and its capability of interpreting phenomena which had been previously looked upon as unaccountable anomalies," I must, in all fairness to my readers, emphasize the fact that much of what is written in Chapters IX and X is purely suggestive. Thus we can easily show that there is a rhythmic gradient down the intestine; we can show that the gradient is upset in a distempered dog; and we can show with excised segments *in vitro* how easy it is to reverse a normal gradient by adding certain poisons like KCN to the Locke's solution. We can speak positively about those things, but we must be careful when we come to say that the reversal found in the sick dog is responsible for the refusal of that dog to eat, and for the inability of his stomach to pass onward the food which has been forced upon him. The observations are highly suggestive; the theory based upon them is proving very useful in explaining the phenomena of indigestion, but we must not lose sight of the fact that it is a theory; that it has weak places, and that much work must yet be done upon it.

As such work will undoubtedly modify or invalidate some of the interpretations which seem logical at this time, it would certainly have been safer and perhaps better if I had left out much of the theorizing which now enters into this little book. By so doing I could undoubtedly have saved myself from future regrets and criticism. I feel, however, with Darwin, that "without speculation there is no good (or) original observation," and that "the observer can generalize his observations incomparably better than any one else." In other words, it would seem that one who has wrestled with a problem day and night for many years, and who has collected all sorts of data bearing upon it, should be most fitted to theorize, to suggest, and to point out the possible applications of his work. He can furnish

the greatest number of jumping-off places for further research; and even those who are incited to prove him wrong may thereby advance the field of knowledge. The only danger is that he and some of his less critical readers may come to regard the suggestions and theories not as a scaffolding for the building of an edifice but as a substantial and finished structure. In this connection a writer may have more to fear from his enthusiastic friends and disciples than from his enemies.

Another danger at this time is that some of the building blocks taken from other edifices to be used now as foundation stones may not bear the strain. I think it was Darwin who said that a theory builder ought really to write to many of the men whom he quotes to see whether they still hold firmly to their published opinions, and whether they approve of the interpretations which he is placing upon their work. It is even better when he can repeat many of the more important and crucial experiments in his own laboratory; and more of that I hope to do in the future. For the present, I can only say that few statements have been made in this book which are not based either upon my own observations or upon a careful reading of several original articles.

I wish gratefully to acknowledge my indebtedness to Dr. Walter B. Cannon who helped me to get started on these problems; to Dr. Saxton T. Pope who aided me with my first little laboratory in San Francisco; to Dr. George H. Whipple, Director of the Hooper Foundation, whose assistance and wise counsel have helped me over many a difficulty; and to Miss Esther Starkweather, Dr. Fletcher B. Taylor and Miss Lucille Mahoney, who have assisted me faithfully with many of the experiments.

WALTER C. ALVAREZ.

SAN FRANCISCO,
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Chapter I

THE AUTONOMY OF THE DIGESTIVE TRACT

THE human mind is not ready to look for new explanations for well-known phenomena, or even to accept them when found, until its contentment with the old explanations has been disturbed. Whenever I describe some of the regional differences in behavior which can easily be demonstrated in the excised stomach and bowel, someone is almost sure to say: "Oh, that is due to the autonomic and the sympathetic." Another says it is a "reflex." So far as they are concerned the matter is settled, and why waste more time on it! When I point out that the peculiarities persist in little pieces of muscle which have been cut out and kept in the ice box for a few days, these individuals take refuge in the fact that there are ganglion cells in Auerbach's plexus.

Now, the most paralyzing thing in scientific work is a facile explanation which puts a stop to further curiosity without really advancing our knowledge of the subject; and I have never been able to see the value of pushing the explanation for a mechanical phenomenon out of the organ in which it might be studied, and into a tiny ganglion where we can hardly follow it. It seems to me that many even of the teachers of physiology have a wrong idea of the nervous system and its relation to the viscera. They look at it some-

what as an electrical power house which not only supplies the motive force but controls the activities, let us say, of the various trains running over a railroad. My analysis of the literature makes me feel that we should look at it more as a telephone switchboard with wires which carry messages of warning and advice from one engineer to another. The trains supply their own power, and the differences in speed and other activities are due to peculiarities in the structure of the engines, peculiarities in fuel, differences in the gradient of the road, etc.

Evolution of the Nervous System. This idea comes out more clearly as we study the development of the nervous system in lower forms of life. First, we have the unicellular organisms which naturally have no difficulty with conduction and do not have nerves. Next, perhaps, come the sponges with muscles but still no nerves. These muscles respond to direct mechanical stimulation transmitted through the overlying epithelium. There is a little conduction from muscle cell to muscle cell, but it is so slow and its spread is so limited that there is no coordination between the movements of adjacent fingers of the sponge (Parker[350]). Next in the scale of development come the animals with nerve nets interposed between the epithelium and the muscles. Such a nerve net in the sea anemone enables the animal, when touched, to contract all over at one time. The stimulus spreads out through the net somewhat as ripples spread from a stone thrown into a pond. If the impulse is slight, only a few muscles will respond locally; but if the impulse is strong, every muscle in the animal will contract (Bethe[55]). A little higher in the scale we find nerve nets which are "polarized," that is, they conduct better in one direction than in another (Parker,[350] p. 130). We shall see later that

Auerbach's plexus is probably one of these "polarized" nerve nets. The trouble with this type of nervous system is that it is uncentralized. There is no single organ to which experiences can be referred or from which volitional impulses can emanate. Moreover, a stimulus at one point is likely to spread all over. These difficulties are overcome in the higher animals by the breaking up of the conducting paths into three relays, consisting of a sensory, a connector and a motor neurone. The connections between these neurones are so made that impulses can pass in one direction only. Furthermore, by means of association fibers, impulses may travel to smaller or larger groups of muscles where they will bring about coordinated movements. The higher the animal is in the scale of existence, the more complicated and more numerous become these association fibers with their valve-like synapses (Parker[348]).

THE FUNCTION OF THE NERVES IS TO EXPEDITE CONDUCTION. It must not be forgotten, however, that in the more complex animals, alongside of the highest type of synaptic system, we find not only the primitive nerve nets, as in the intestine, bladder and arteries, but we find evidence of the original protoplasmic transmission from cell to cell. Similarly, in a modern city we find, alongside of the telephone, the original messenger boy. The thing to be kept in mind is that the nervous system in all its stages of development has one big function, and that is to expedite conduction. Loeb[270] has shown by numberless experiments that there is no storage of wisdom in ganglia and "centers." He takes up one complicated reflex after another; he takes up "purposeful reactions" and "instincts," and shows that they are due simply to localized peculiarities of structure and chemical affinity.

All sorts of properties have been ascribed to the ganglion cells, but it appears now that these structures serve more as nutritional centers for the nerve fibers than as storehouses of wisdom and tone. Bethe[54] (p. 403) was able by microdissection to trim off all such cells from the nerve bundle going to one of the antennae of a small crayfish, and found no difference in the tone and reflex irritability of the muscles in that antenna. This suggests strongly that the reflex impulses do not even have to pass through the ganglia, let alone originate in them. Similarly, if we remove the central ganglion from an ascidian, its complicated reflexes are still carried out. The only difference is that they need a stronger stimulus and they are executed more slowly because conduction is then effected through the nerve net (Loeb,[270] p. 35, Jordan[221]). Most of us think of the pupillary response to light purely as a complicated cerebral reflex, but it has been shown that not only does the pupil of the excised eye react, but small muscle bundles cut out from the iris will respond directly to the stimulus of a strong light (Parker,[350] p. 51). Even more remarkable is the fact that a beheaded shark can swim as if there were little the matter with him, and a frog can catch flies, swallow and digest them for weeks after his forebrain has been removed.

Many other examples might be given of the simplicity of the mechanisms which bring about complicated and purposeful reactions in small excised segments of animals, but we must hurry on to an analysis of the problems in the particular field under discussion—the intestine.

The Autonomy of the Digestive Tract. We find, as might have been expected, that after the preliminary shock wears off digestion goes on quite well after section of the vagi and the splanchnics (Cannon,[81] Rubaschow,[379] Krehl[241]).

That observation has been made by so many physiologists that there can be no question about it. Furthermore, peristalsis and strong rhythmic contractions can be obtained in the excised stomach and intestine, either perfused or placed in oxygenated Locke's solution; in short segments of bowel, and even in bits of muscle removed from the wall. It is clear, then, that the gastro-intestinal tract is largely autonomous; that is, it carries within itself the mechanisms essential to peristalsis. This point cannot be emphasized too strongly, because it seems to me that the failure to grasp it is the greatest stumbling block to further advance in our understanding of the subject. It is undoubtedly true that the extrinsic nerves have much to do with peristalsis both in health and disease, but it is very helpful in simplifying our problems to recognize that the tract can get along without any outside help or interference. This should make us the more willing and eager to study the all-important local mechanisms.

Chapter II

THE MYOGENIC NATURE OF THE RHYTHMIC CONTRACTIONS AND THE FUNCTIONS OF AUERBACH'S PLEXUS

HAVING established clearly that the digestive tract is highly autonomous, and that the mechanism producing peristalsis is to be found in the wall of the gut, the next question is: Which of the two structures in that wall is the more important—the muscle or the nerve net? On turning to the various textbooks on physiology we find the definite statement made that the rhythmic contractions of the bowel are neurogenic, and due to stimuli coming from the ganglion cells in Auerbach's plexus. The writers all base this opinion on the second and fourth papers by Magnus[290] and[292] who found that when he stripped the longitudinal muscle from the circular, the plexus always came away with the former because it lies protected there in little grooves. His microphotographs of the adjoining surfaces of the two muscle coats show on one side the plexus practically intact and on the other only a few isolated fragments. As he says, "*Auf der freigelegten Oberfläche der Ringmuskulatur der Auerbachsche Plexus entweder garnicht vorhanden ist, oder nur ganz geringe Bruchstücke oder ganz vereinzelte Knotenpunkte davon nachweisen lassen*"[290] (p. 357).

The thing which impressed him was that the longitudinal muscle, with the nerves, contracted rhythmically, while the circular did not. Moreover, the circular muscle differed from the longitudinal in that it could be tetanized and that

it had a refractory period.[291] These differences were so striking that Magnus felt no doubt about the neurogenic origin of the rhythmic contractions; and his positive statements have been quoted unhesitatingly ever since. Unfortunately, few physiologists seem to have noticed that in Magnus' later work he ran into serious perplexities. We find in his fifth paper[293] the admission that when he added a little pilocarpin, strophanthin or barium to the Locke's solution he got good rhythmic contractions not only in the longitudinal strips but also in the carefully denervated and previously quiescent circular ones (Fig. 1*A*). At first he thought that this was due to some effect of the drugs on remnants of the plexus left on the outer surface of the muscle, so he seared that surface with crystals of silver nitrate. This treatment put an end to the rhythmic contractions even in the presence of pilocarpin, strophanthin and barium, but segments which reacted in a typically denervated way with these drugs still contracted rhythmically under the influence of physostigmin. He remained satisfied that these segments were thoroughly freed from the plexus but still seemed to feel that the fact that the rhythmic contractions were brought out by a drug made them a little different from the normal ones. He was not so surprised at the action of physostigmin because he had observed previously in a marine worm that when the nervous system was completely removed (easily done on account of the large size of the fibers) the muscles would contract rhythmically in weak solutions of that drug.

Certainly, it is remarkable that when a worker publishes negative results, and later positive ones, the negative results should become one of the corner stones of physiology, upon which opinion remains unanimous.

It is the more remarkable when we note the large amount

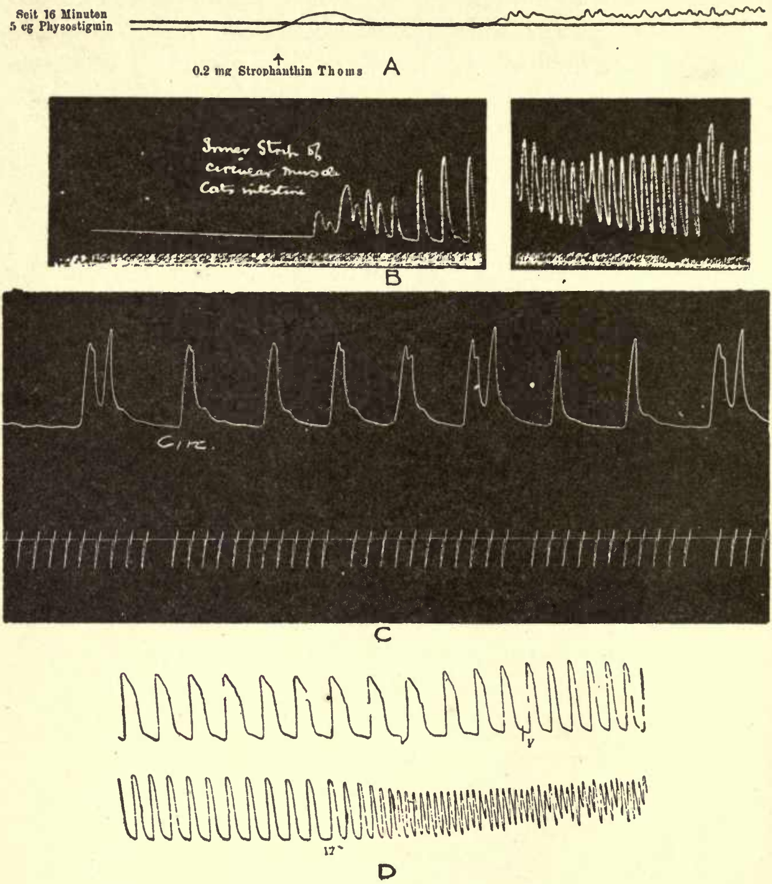

FIG. 1.

(*A*) Plexus-free preparation contracting rhythmically. (*From Magnus.*)

(*B*) Denervated muscle. (*From Gunn and Underhill.*)

(*C*) Tracing from one of my own experiments with denervated muscle.

(*D*) Rhythmic changes in the evolution of hydrogen when acids act on chromium. Note increase of rate with rise in temperature of the solution. (*From Ostwald.*)

of evidence from other workers, showing that muscle alone has a strong tendency to rhythmic contraction. It is remarkable again that no one seems to have paid any attention to the excellent paper by Gunn and Underhill,[174] who repeated Magnus' work with great care. They cut down the shock by making the dissection in iced Locke's solution, which acted as an anesthetic. Instead of searing the outer surface of the muscle to remove all vestiges of the plexus they stripped off only a few fibers from the mucous membrane side and used those for their experiments. In this way they obtained muscle which certainly must have been plexus-free and which contracted rhythmically, as can be seen in Fig. 1*B*, copied from their article.

Remembering that the intestinal muscle from the dog often contracts better after from one to three days in the ice-box, Miss Mahoney and I repeated Gunn and Underhill's work, using segments of duodenum twenty-four hours old; and even without the precaution of keeping the tissue cold, we found little difficulty in getting rhythmic contractions from strips of circular muscle. Although Magnus says he waited hours, it may be that his failures could have been avoided by waiting longer. We find that some strips will start beating only after they have been for six or seven hours in the solution. This period of waiting can be shortened greatly by adding a trace of barium to the solution. The effect of this drug is generally the same on the longitudinal as on the circular strips. After obtaining these records, the strips were examined histologically, and in some of them it could be proved that only the inner half of the circular layer had been used.

I feel, therefore, that we must admit that the smooth muscle of the intestinal wall shares in that tendency to rhythmic contraction which is seen so universally in muscular

tissue. This is what we should expect when we remember that strips of intestine beat even better on the second or third day than on the first. I have records showing that the rate is even faster and the rhythm more regular on the second day (Alvarez[10]). When we remember that some sympathetic ganglia fail to function within a few minutes after the circulation ceases, it is hard to believe that in the bowel their functions can actually improve after death. It is much easier to believe that the improved contractility is due to the removal of nervous inhibitions, and to the wearing off of the shock of cutting. Moreover, Bayliss and Starling[39] (p. 138) found that cocain applied to the surface of the bowel abolished the myenteric reflex and with it the power of the bowel to pass on a bolus. It improved, however, the amplitude and regularity of the rhythmic contractions. As nicotin had exactly the same effect when injected repeatedly and in large doses, they had good reason to infer that they had paralyzed the plexus; that the myenteric reflex is due to the nerves, and that the rhythmic contractions are due to the muscle. Although I am rather prejudiced against physiologic conclusions based on the assumed selective action of poisons, it does seem to me that we must face this evidence squarely. Certainly, we cannot go on quoting these experiments to show that the progress of food through the bowel is based on a nervous mechanism, and Magnus' experiments to show that the rhythmic contractions are also based upon it. If Bayliss and Starling were right Magnus was wrong, and vice versa.

When one remembers how common rhythmical processes are in nature it is hard to understand why physiologists tend so often to ascribe those observed in muscle to that highly specialized organ, the nervous system. Curves closely resembling those traced by a frog's heart can be

produced by a simple physico chemical reaction (Fig. 1*D*). These tracings from Ostwald's[347] article were produced by attaching an ordinary tambour to a flask in which hydrochloric acid was acting on chromium with the evolution of hydrogen. Rhythmic changes take place in the metal which make it alternately resistant and subject to attack by the acid. Similar rhythmic changes occur in the rate of catalytic decomposition of hydrogen peroxide in contact with mercury, owing to the alternate formation and dissolution of a surface-film of "peroxidate." In both of these reactions electricity plays a large part, much as it does in the animal body. When water drips at regular intervals from a reservoir we have a rhythmic response to a constant force. Forbes and Gregg[154] have remarked upon several instances of this type of reaction in the body. Quincke produced rhythmic alterations in the shapes of air bubbles trapped under water and placed in the path of a fine stream of alcohol (Loeb,[270] p. 22). The pulsations of the bubble closely resemble those of a heart, and are due to alterations in the surface tension. Turning from these purely chemical and physical phenomena we learn that Bose[66] has observed beautifully rhythmic contractions in the leaflets of certain plants. A little higher in the scale, we find animal tissues, not yet muscular in structure, but possessing the power of rhythmic contraction. I need only mention cilia and the tails of spermatozoa.

The heart beat seems to originate in muscle or muscle-like tissue except in the Limulus, a very primitive type of crab; and even in that animal, Garrey[157] has shown that the denervated muscle will contract rhythmically if put into N/2 NaCl. The heart of the embryo chick beats after twenty-nine hours of incubation, although nerve cells do not reach it until the sixth day (Parker,[350] p. 55, Verzar[439]);

and even the isolated heart muscle cells in tissue cultures have been observed to beat (Burrows[78]). The same thing was seen by Lewis and Lewis in cultures of smooth muscle.[264] The retractor penis of the dog is made up of smooth muscle; it has no ganglia (Fletcher,[151] Fisher[150]) and yet it contracts rhythmically when excised (De Zilwa,[454] Edmunds[133]). Loeb has shown, moreover, that even striated muscle will contract rhythmically in the proper concentration of NaCl (Loeb,[271] p. 78, Mines[321]). Hydromedusa stops pulsating when the nerve net is excised, and this was supposed to prove the nervous origin of the beat until Loeb,[270] p. 18) showed that the muscle will start up again if the concentration of the sea water is changed. Romanes found, moreover, that the nerveless center of another type of jellyfish, Acalepha, will beat in sea water.

It is clear, then, that although some forms of muscle do not beat rhythmically by themselves when immersed in their body fluids or in Locke's solution, they will beat when placed in a suitable medium. As the denervated intestinal muscle will beat in Locke's solution, I see no reason for saying that it is normally dependent upon Auerbach's plexus for its rhythmic stimuli. About the only evidence that I know of now in favor of the neurogenic origin is that presented by Yanase,[453] who observed peristalsis in embryo guinea pigs only after the twenty-sixth day, when the myenteric plexus and the longitudinal muscle appear. This negative evidence is not conclusive for a number of reasons.

Although the muscle can contract rhythmically by itself it is normally in close relationship to its nerves. As Gaskell[160] (p. 105) says, these nerves are there for a purpose and the muscle contracts better for their presence. In actual life it makes little difference which one has the more to do with

the rhythmicity because they both work together; and the only reason I have devoted so much space to the matter is that the acceptance of the neurogenic explanation for the activities of the bowel causes the student to lose sight of the great need for studying the regional peculiarities of the muscle.

THE FUNCTION OF AUERBACH'S PLEXUS. The next question is, if the muscle can contract by itself, what is Auerbach's plexus good for? It almost undoubtedly serves for the conduction of stimuli and the coordination of movements. A centipede is a colony of legs each segment of which can walk and attend to its own affairs. Normally they all follow the lead of the head segment. If we cut the nerve cord we get, in effect, two independent centipedes, one of which may want to stand still while the other wants to walk off. The result is that the animal turns from time to time to bite savagely at its rear half which it seems to regard only as a foreign body (Carlson,[94] p. 286). The hind end of a planarian worm which has grown too long for efficient conduction fails to follow the lead of the front end. It takes firm hold of the aquarium wall; the front end crawls on unconcernedly, and the worm is pulled in two (Child,[111] p. 131). We would probably have similar conflicts in the bowel, with colic and dynamic ileus as a result, if rapid conduction were not possible through the myenteric plexus and through the nerves in the mesentery. My own measurements indicate that impulses travel about 20 cm. per second through the plexus (Alvarez and Starkweather[18]). This seems pretty slow for nervous transmission, but it must be remembered that these nets represent early stages in the evolution of conducting tissue, and the rate in the bowel is very similar to that observed in the nets of some of the lower organisms

(Lillie,[266] p. 417; Jenkins and Carlson,[215] Hecht,[181] Parker,[349] p. 231). The rush waves in the bowel which travel from muscle fiber to muscle fiber cover about 4 cm. per second in the rabbit. Impulses through the mesenteric nerves seem to travel about 200 cm. per second. The existence of such extra-mural means of transmission has been proved by obtaining responses to stimulation on the farther side of gaps in which the bowel has been removed (Mayer,[304] p. 451; Kirschner and Mangold,[236] p. 491; Roith,[375] Marbaix,[300] p. 283; Surmont and Dubus[417]).

Another function of Auerbach's plexus is probably to make the muscles respond properly to stimuli coming from the under-lying mucous membrane. These stimuli are collected by Meissner's plexus and transmitted to Auerbach's by connecting fibers. Cannon[86] (p. 184) and Jacobj[213] have remarked that the peristaltic movement seem to be modified continually by the chemical nature of the intestinal contents; and we know that inflammation of the mucous membrane and its irritation by certain purges will give rise to heightened peristalsis (Katsch and Borchers,[228] p. 237). On the other hand, pricks from sharp foreign bodies like pins within the gut are said to inhibit the overlying muscle so that perforation will be avoided (Exner,[145] A. Müller[333]).

Still another function of the plexus is probably to keep the muscle from being too active (Bayliss and Starling,[41] p. 133) or from contracting down into a hard knot. It is well known to experimental zoologists that when smooth muscle is cut off from its nervous connections its tone is likely to rise to a point where rhythmic contractions are no more possible (Magnus,[289] Jordan,[220] p. 210, Biedermann[58]). Magnus' difficulty in getting good records from the denervated circular muscle was due probably in part to the spasmodic contraction which appeared when he removed the

plexus. Similarly, Cannon[81] (p. 432) observed a remarkable shrinkage of the stomach into a hard narrow tube when he cut the extrinsic nerves. The condition corresponds somewhat to that seen in the spastic paralyses of the voluntary muscles in man after cerebral hemorrhages. It may easily be that some of the contraction rings seen in spasmodic ileus, in infantile pyloric stenosis, and in Hirschsprung's disease are due, not to an excess of nervous stimulation but to an absence of it.

Many have assumed that Auerbach's plexus serves to bring about reflexes in the intestinal wall, but this seems unlikely because neither the anatomists nor the physiologists have been able to demonstrate the requisite nervous arcs. A recent attempt to show them with the help of strychnin also failed. That drug was chosen because it seems to act mainly on the synapses between neurones: it closes the gaps, lowers the threshold and exaggerates reflexes (Porter[363]). Moore has pointed out that we can probably judge of the part played by synapses in any particular organism's nervous system by the extent to which it responds to strychnin (Moore;[325] Knowlton and Moore;[238] McGuigan and Becht;[314] McGuigan, Keeton and Sloan;[315] Sherrington,[397] pp. 42 and 111). The simpler animals with pure nerve nets hardly respond at all. It is very suggestive, then, that Miss Starkweather and I could find no difference in the reactions of either the intact or excised bowel before and after giving lethal doses of strychnin (Alvarez and Starkweather[18]). Apparently the myenteric plexus is a fairly simple nerve net without synapses, "centers" or reflex arcs. As I said before, its principle function, like that of the nerves elsewhere, is to expedite conduction.

CHAPTER III

THE SMOOTH MUSCLE OF THE GASTRO-INTESTINAL TRACT

I HAD not been working long on the problems of peristalsis before I became impressed with the need for learning everything possible about smooth muscle. More and more it seemed to me that if I knew just what that tissue would do under certain conditions I could explain many of the activities of the gut. I felt still surer of that when I found how autonomous the muscle is, and how strong its tendency is to contract rhythmically, even in the absence of nervous stimuli. It would seem well, then, in this chapter to enumerate briefly some of the properties and pecularities of smooth muscle. Although from now on the term *muscle* will often be used, it must not be forgotten that there are nerve cells scattered amongst the contractile fibers, connecting them together and modifying their reactions. To be exact, we should probably use the term *musculoneural apparatus* except in those instances in which we refer to denervated muscle, but the word is long and unwieldy, and after this explanation, I think it will be safe to use the shorter term *muscle.*

As is well known, smooth muscle is made up of spindle-shaped cells which vary in size, shape, number of nuclei, etc., in different animals and in different parts of the same animal (Ranvier,[369] p. 433, Pompilian,[362] Lapique,[253] McGill,[313] Schultz,[390] Bottazzi and Grünbaum,[70] Paukul,[353] Schiefferdecker[385]). As a rule it contracts more sluggishly

than striated muscle does; it takes longer to get started, and it is slower in recovering its original length. Incidentally, the greatest difficulty in working with this type of muscle arises from the fact that one can never be sure what its original length was because of the constant tone changes. After a number of strong stimuli or sometimes after only one, the muscle may become quite refractory (Parker,[350] p. 168, Jennings,[216] Woodworth,[451] p. 39), but after a long rest it seems to get on a hair trigger again so that it responds powerfully and explosively to a slight stimulus. That is the condition of the digestive tract after the night's rest; and it probably has much to do with the fact that most of us have the daily bowel movement in the morning, immediately after breakfast. With an animal open under salt solution, one can often start a rush wave down the bowel by pinching the duodenum. For some time afterwards, similar pinches will have no effect, but if we wait long enough we will again find the bowel so sensitive that the slightest stimulus will start a wave.

Another characteristic of smooth muscle is its ability to maintain a firm and lasting contration without fatigue. We see this in the muscles which close the shells of bivalves, and we see it in the wall of the colon. It is interesting that the muscle in a bivalve consists of two parts: one which closes the shell and the other which locks it closed. By cutting first one and then the other it can be shown that neither one can do the work of the other (Parnas[351]). Similarly, if a man of average strength tries to hold his arm out perpendicularly to his body he soon finds it a most painful and fatiguing experiment. The deltoid was not designed for such heavy work, but the glutei and back muscles are carrying much heavier loads all day and they do not complain (Sherrington,[398] p. 191). We learn from this

that there are all kinds of muscles, all suited to different purposes. Some, like those in the wings of insects, must contract 300 times a second; others like those in the wings of a hen have little to do. Those who think all muscle is the same forget the differences between the white and dark meats of chicken, between the heart and the gizzard; between tenderloin, roundsteak and tongue. I have gone into these differences so at length because I believe there are similar differences between the muscle in the cardiac and pyloric ends of the stomach (Alvarez[5,6,7,8]); between that in the small intestine and that in the cecum (Alvarez and Starkweather[13]) and colon (Alvarez[10]). The muscle on the lesser curvature near the cardia is soft to the touch like coagulated fibrin; that in the pyloric antrum is tough like gizzard and has a different color. If we stimulate the two with an electric current or with a pinch, we get two entirely different contraction curves; and if we put them into warm oxygenated Locke's solution we get two different types of rhythmic activity. These differences should be expected when we remember that the upper and lower ends of the stomach have different kinds of work to do. The upper end serves largely as a hopper to hold the food; the lower as the mill to do the heavy work. More of these local peculiarities will be described later.

Another characteristic of smooth muscle in hollow organs is its responsiveness to tension. Most of the motor activities of the stomach and bowel are brought about and regulated largely by the internal pressure due to the presence of food or gas. Cannon[86] (p. 187) has shown that the rhythmic segmentation in the small intestine is due simply to the fact that those muscle fibers which are stretched tend to contract. Their contraction increases the pressure in neighboring segments, and so the process goes on. Cannon has shown also that the waves in the stomach tend to appear at those

places where the internal pressure balances the local tone of the muscle. If the pressure is too little or too great there may be no waves (Cannon,[86] p. 189, Straub,[414] Wislocki and O'Connor[449]). We know also that when a man has been purged, his bowels are not likely to move for a few days. This has been supposed to be due to an astringent or constipating action of the purge, but I have considerable evidence to show that it is due simply to the lack of tension in the colon. The bowel has to fill up to a certain point before the muscle fibers will be stretched enough so that they will contract well. As Cannon points out, these reactions to stretching are purely local and are not brought about by nervous reflexes.

Smooth muscle shortens also under the influence of direct irritation. Thus we find spasmodic contraction of the cardia, pylorus, ileocecal sphincter and anus when there is ulceration or inflammation near by. We find hourglass contractions of the stomach opposite ulcers on the lesser curvature; and shrunken and irritable caps with ulcers in that region. From a diagnostic standpoint it is unfortunate that carcinomatous tissue often fails to stimulate the muscle in this way. Particularly in the colon, where the muscle is most sluggish, carcinomas will often remain symptomless until they block the lumen mechanically. Some of the sphincter spasms that are seen with inflammations or ulcers in various parts of the digestive tract may be due simply to a greater irritability of the sphincters as compared with the rest of the gut. With a lower threshold they would be very likely to pick up, and respond to stimuli which are ineffective for adjacent muscle fibers. As I shall point out later in Chapter VIII, the muscle fibers in the pyloric sphincter actually are more irritable than the fibers in the rest of the antrum (Alvarez,[6] p. 326).

Those who would like to go more fully into the physiology of smooth muscle can get an entrée into the subject by reading the encyclopedic articles of Grützner[171] and Schultz[390, 391]).

The following chapter deals with the peculiarities in peristalsis found in different parts of the digestive tract, peculiarities which are shown to be due largely to local differences in the structure and physiological properties of the musculo-neural apparatus.

Chapter IV

THE DIFFERENT TYPES OF PERISTALTIC ACTIVITY

BEFORE taking up the problem of peristalsis it will probably be helpful to review briefly the different types of contraction which appear in different parts of the digestive tract. We can do this systematically by following the progress of a barium meal from the mouth to the anus. The mouthfuls shoot through the first part of the *esophagus* largely because the muscle there is striated and quick-acting. In the lower third, the muscle is largely of the smooth variety and progress is slowed. Not infrequently powerful contractions near the cardia can be seen to throw the food back towards the mouth.

In the *human stomach,* waves appear about once in twenty seconds. As will be shown in Chapter VIII, carefully taken serial plates reveal the fact that these waves begin near the cardia. They travel as shallow ripples until either proper pressure conditions or the presence of the peculiar antral muscle causes them to break into deep waves. Ordinarily we see only one or two waves at a time, but in the presence of a diseased gallbladder or an ulcerated duodenum the stomach often gets so irritable that four or five deep waves course over it at one time. Reverse waves are seen only under pathological conditions. During the first stages of starvation there appear the powerful, so-called hunger contractions (Carlson[96]).

The gastric waves do not cross the *pylorus* so far as we can see. As I shall point out later, there is some evidence that an impulse or wave of some kind does cross over to give rise perhaps at times to the peristaltic rushes in the small bowel. This block seems to be due partly to the anatomical peculiarities of this region (Cunningham,[123] Brinton,[73] p. 268) and partly to the physiological differences which, as we shall see later, exist between the muscle in the pyloric antrum and in the duodenum. According to Aufschnaiter,[25] the circular muscle of the stomach thickens at the pylorus to form a swelling in which the little bundles of fibers are more or less braided. This swelling is divided into a number of sections by connective-tissue partitions running from the peritoneum to the mucous membrane. One of these partitions is so complete that there is little muscular connection left between the stomach and the duodenum. Most of the fibers in the outer longitudinal layer of the stomach dip down into the pyloric swelling, and only a few run over on to the duodenum. Toldt[428] believes that these partitions of connective tissue and longitudinal muscle are remnants left behind during embryonic life when the pyloric swelling is formed by an infolding of the wall of the primitive gut. A few of the circular fibers from the pyloric ring run down over the duodenal cap in a festoon-like arrangement, some of them becoming almost longitudinal in direction. The connective tissue barriers at the pylorus have been described by one or two other anatomists (Todd,[427] p. 84) and they may easily interfere with the passage of waves. We shall see later, however, that gastric and intestinal waves can jump connective tissue gaps resulting from operations, so it seems to me that the main cause of the block must be the difference in the physiological properties of the muscle in the stomach and in the duodenum. Lillie[268] (p. 177) and

again[266] (p. 439) and others have pointed out that a stimulus suited to the metabolism of a sluggish muscle will often have no effect on a quick-acting one, and it may be that waves coming every twenty seconds cannot spread well into a tissue which contracts rhythmically with a period of three seconds. There is still another possibility, and that is that the greater irritability of the sphincteric muscle causes it to contract and to get into a refractory condition before the main part of the wave gets to it. There is a great deal of evidence to show that a wave of electrical disturbance travels ahead of the visible contraction wave; and time and again while watching gastric peristalsis in animals and in man it has seemed to me that the irritable pyloric ring responded sufficiently ahead of time so that it served to block the oncoming wave.

The *duodenal cap* tends to remain filled during the early stages of digestion. This may be due to the low rhythmicity of the muscle in that region (Alvarez,[10] p. 344), to its thinness and weakness (in man), to its firm attachment to the mucous membrane, and perhaps to the peculiar festoon-like arrangement of the fibers mentioned in the preceding paragraph (Aufschnaiter,[25] Verson[438]). Particularly towards the close of gastric digestion there is normally some regurgitation of duodenal contents into the stomach. Once past the cap, the food runs rapidly through the rest of the duodenum and jejunum. The jejunum is jejune or empty probably on account of its great irritability. The barium mixture in that part of the bowel moves so rapidly that it appears to be sprayed over the folds of the mucous membrane. In the lower ileum its progress is slowed and the barium meal can be seen lying quietly in dense sausage shaped masses.

We see from time to time in the *small bowel*, and particu-

larly in the jejunum, rhythmic movements which serve to mix the food intimately with the digestive juices and to move it back and forth over the absorbing surface. If these contractions are spaced two or three centimeters apart we have what Cannon calls "rhythmic segmentation" (Fig. 2). That is seen often in the cat, and I have observed it also in man. (See also Kästle and Bruegel.[223]) In the rabbit and also

FIG. 2.—A photograph of the small intestine during rhythmic segmentation. (*From Cannon.*)

in man the contractions may appear five or ten centimeters apart, and the food is then thrown rhythmically from one end of a short loop to the other—"*Pendelbewegung*" or pendulum movement; also "*Mischbewegung*" or "*Knetbewegung.*" These kneading movements are brought about by local conditions of tension, and they have little to do with the forwarding of food down the bowel. Experiments on dogs with Nella's fistulae show that they will move material at the rate of one centimeter in from a minute to an hour (Cash,[108] Fubini[156]). Most of the forwarding is brought about by the "*Rollbewegungen,*" "*Schubbewegungen,*" "*Forderungsperistaltik,*" or "peristaltic rushes" which appear from time to time. These may seem to arise in any part of the

small bowel and may run either short or long distances. In diarrheic rabbits I have seen them go from the duodenum to the anus. My graphic records show, however, that even

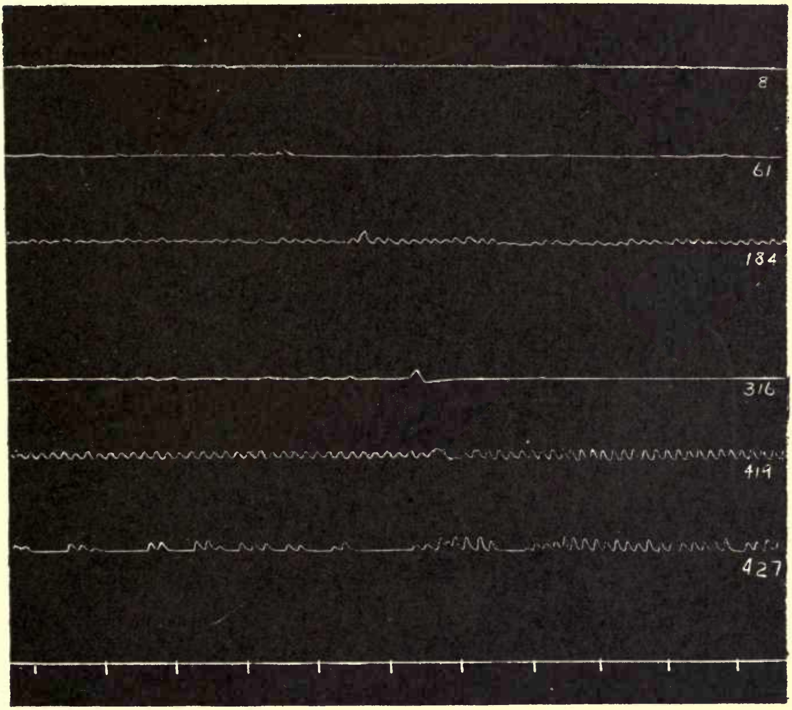

Fig. 3.—Tracing from six recorders on a rabbit's small intestine. The amplitude of contractions is small in the duodenum. A diastaltic wave may be observed in its progress from one end of the small intestine to the other. Time markings show thirty-second intervals. The figures at the right represent distances from the pylorus, in centimeters.

the short rushes which, so far as the eye can see, have arisen in the lower ileum, are generally based upon ripples which have come from the duodenum (Alvarez[3]—Fig. 3). As

some of these ripples can be shown to have left the first portion of the duodenum just after a gastric wave reached the pylorus, it may easily be that they had their origin as high as the stomach. In a few instances they followed closely on swallowing movements, which suggests that their origin may be even higher than the stomach. (See also Esslemont.[143]) The graphic records show also that the emptying of the small bowel into the large, and often the defecation movements are timed by the arrival of the ripples.

These rush waves serve to move onward the material which has been segmented rhythmically for some time at one point. Often as one bolus moves forward another moves down to take its place, much as the players in a baseball game shift when the bases are full and the man on third goes "home." The rush waves tend to be stopped by active contractions which appear ahead of them. If this were not so the bowel would rapidly be emptied, and the animal's nutrition would suffer.

The slowing of the intestinal contents above the *ileocecal sphincter* is due partly to a tendency towards reverse peristalsis in that region (Alvarez,[2] also[3]). In the rabbit, the reverse waves arise in the sacculus rotundus, a rudimentary cecum surrounding the sphincter; in the cat, and probably in man, they arise in a sort of accessory sphincter: a thickening of the last few centimeters of the muscular coat of the small intestine (Luschka,[283] Keith,[229] Elliott,[136] p. 158). Its action is much like that of certain muscular rings which take the place of tight sphincters in lower forms of life (Bottazzi,[67] p. 481, and von Brücke,[75] p. 202). Were it not for this mechanism the food would probably be rushed into the colon too rapidly. It must not be forgotten, then, that the sphincter has two functions: one to restrain the material

coming down from above, and the other to prevent regurgitation of colonic contents into the ileum.

Hurst[203] (p. 54) noticed years ago that after stagnating for some time above the sphincter, the ileal contents tend to empty into the colon immediately after the taking of food. I have observed this "gastrocolic" reflex many times. Lyman[284] has described a "receptive relaxation" of the colon for ileal emptying similar to that of the stomach when food is coming down the esophagus (Cannon[86]).

In all this discussion I have used the term "sphincter" instead of "valve" because it seems to me that even in man the closure is due mainly to a muscular puckering. Rutherford[380] and others who have been able to observe the human sphincter through large cecal fistulae maintain that, when in action, there is no sign of the lips which appear in dissections; instead, there is a symmetrical rosette. We know that the lip-like structure is not essential to health because people get along very well after ileocolonic anastomoses which are often made very crudely. We know also that the bear, ferret and hedgehog get along perfectly without any sign of an ileocecal sphincter (Elliott[136]).

The spontaneous regurgitation of colonic contents is observed very rarely in man, but it is quite commonly observed after the giving of barium enemas (Dietlen,[128] Case,[104] pp. 45, and,[106] pp. 380 and 383). Although in some of these cases it indicates disease, it is probably more often due to the abnormal conditions brought about by the unusual distention of the colon. Cannon,[86] (p. 156) found in cats that large enemas were passed back into the small intestine while small ones were not. In this connection it is interesting to quote Senn's[396] (p. 224) statement that air under a pressure of 2½ pounds per square inch can be passed from the anus to the mouth in man.

The physiologist must be interested also in the fact that the waves in the ileum and in the colon tend to stop at the sphincter. In trying to explain this blockage we can turn to the same three arguments used in the discussion of the pyloric block. Here again we have a certain amount of plication and interruption of the muscular coats—apparently not so marked as at the pylorus. Engelmann and Van Brakel[141] and Verson[438] speak of a connective tissue barrier, but the illustrations of Rutherford[380] do not show it. Toldt[428] shows that a layer of longitudinal muscle from the ileum runs out nearly to the tip of each valve lip between the two layers of circular muscle, one of which comes from the ileum and the other from the colon. (See also Luschka[283] and Lebon and Auburg.[256]) There is, moreover, a difference in the type of muscle above and below the sphincter, similar to that above and below the pylorus. There is also the sphincteric muscle which, probably on account of a greater irritability, contracts in front of and blocks advancing waves of reverse peristalsis in the colon. In the rabbit I have often seen strong peristaltic rushes crossing from the ileum to the colon without any delay at the sphincter. Ordinarily, however, even the rush waves stop in the terminal ileum. Heile[183] has observed that stimulation of the colon will slow the passage of material through the sphincter.

There is one more peculiarity of the muscle in both the pyloric and ileocecal rings and that is that it contracts under the influence of adrenalin (Elliott,[136] p. 157, also,[137] p. 416; and Kuroda[246]). Gaskell[160] (p. 46) has offered an interesting explanation of this unique behavior; and it may be that the inclusion of these peculiar rings of muscle has something to do with the blocks in their neighborhood.

The muscle in the *colon* is sluggish and waves of contraction appear only at long intervals. In the rabbit the haustra

show a fairly rapid and peculiar type of rhythmic contraction which I can only liken to the weaving movements of the two jump-ropes used by children. The wave coming from the left margin (as one looks at a haustrum) moves clockwise and the one from the right edge moves anticlockwise. While watching these movements one is made to think also of the roll tops of two desks facing each other. First one top is pulled down and then the other. Hurst and Newton[205] claim to have seen similar movements in man, but they must certainly be rare. Kastle and Bruegel[223] took cinematographic plates of the colon in man and observed very

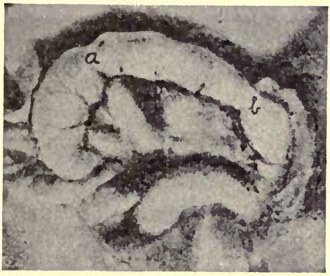

FIG. 4.—Photograph of a colon exposed under warm salt solution. Tonus ring *b* is sending forth antiperistaltic waves, which are stopped by the nearly relaxed tonus ring *a*. (*From Cannon.*)

little movement. They describe several types of slow haustral contractions. In man, forwarding movements appear probably only a few times a day. These were described by Hurst in 1907[197] (p. 423) and in 1908[198] (p. 9); Holzknecht[192] in 1909; by Barclay[32] in 1912, and later by Hurst and Newton,[205] Case[106] (1915), and others. I have seen them several times, generally in people with a tendency to diarrhea. The haustra relax, a sausage-shaped mass is formed, usually in the transverse colon, and this is rushed quite rapidly

toward the rectum. In the cat and dog, defecation is brought about ordinarily by a marked shortening and a powerful contraction of almost the whole colon; in man the process is confined almost entirely to an emptying of the sigmoid and rectum.

Reverse peristalsis is a normal activity in the right half of the colon in a number of animals (Sanders,[382] Jacobj,[212] p. 147; Cannon,[86] p. 152 and[80], p. 265—Fig. 4). It has been observed in man (Case,[104] and,[107] p. 687, but there it is hard to demonstrate; and the waves certainly do not correspond in activity and depth to those seen, for example, in the cat. Kastle and Bruegel[223] could not show it in their cinematographic studies. As Cannon has shown so beautifully, the reverse waves in animals often start from a pulsating contraction ring. They run for a while, and then alternate with downward waves.

Reverse transport of material is observed not infrequently in the lower colon when defecation is postponed (Schwartz,[394] Case[106]). Under those conditions feces may move back into the sigmoid or descending colon. The reverse transport of material in the colon after ileosigmoidostomy is now well known.

SUMMARY

The point that I wish to emphasize in the foregoing discussion is that there are several types of intestinal movement—types which must be distinguished clearly or misunderstandings will arise. They may be recapitulated briefly as follows:

Stomach—Regularly recurring waves running from cardia to pylorus. Reverse peristalsis pathologic.

Small Intestine—Rhythmic segmenting or kneading movements which have little to do with forwarding the

contents. Occasional rush waves which move food for shorter or longer lengths through the bowel. Reverse peristalsis, probably pathologic, except towards the close of gastric digestion when duodenal contents normally regurgitate into the stomach. Perhaps some normal reverse peristalsis in the terminal ileum.

Colon—Sluggish local contractions and haustral movements. Rush waves at long intervals. Reverse peristalsis physiologic, particularly in the right half of the colon.

Cannon and others have invented the following names for these different manifestations:

Peristalsis—A general term for intestinal movements.

Katastalsis—Normal downward movements in stomach or colon.

Diastalsis—Through- or rush-waves in the small bowel.

Anastalsis or Retrostalsis—Reverse peristalsis.

If the stomach is cut out and put in a warm moist chamber or in Locke's solution, waves may go over it just as they do in the intact animal. If a loop of small intestine is similarly treated, rhythmic contractions appear now here, now there along its length. One part does not set the pace for another, and only rarely can one see waves traveling from one end of the loop to the other. If a short segment is fastened to a little lever it will contract regularly at a rate which corresponds to that of the rhythmic segmentation in the region from which the piece was removed. That rate varies inversely as the distance from the pylorus.

In the discussion which makes up most of this book I shall be concerned mainly with the diastaltic and anastaltic types of waves which move food from one end of the stomach or bowel to the other.

Chapter V

GRADIENTS

IF, at a certain point, we stimulate the smooth muscle in a tubular organ like the intestine or ureter, we get a contracted tonic ring from which waves are given off in both directions (Cannon,[84] and,[87] p. 419; Engelmann,[140] p. 259; Kretschmer[243]). These waves remind one of the concentric ripples which arise at the point where a stone has been thrown into a pond, and actually the physical conditions underlying the two phenomena are very similar. In each case the level or potential is raised at one point and waves of activity flow down away from that region until an equilibrium is restored. If another stone is thrown into the pond near the first one, some of the waves approaching the second area are slowed and stopped; and similarly, if a second tonus ring is made in the bowel, the waves approaching it are blocked. They are slowed and stopped because they have, in a way, to run up hill to the second area of high potential. One of the best ways in which to make one of these pulsating contraction rings is to touch the bowel with a crystal of barium chloride which, as is well known, raises the tone of the muscle.

Conduction. These waves spread out from muscle fiber to muscle fiber, and there is little need for any assistance from nerves, ganglia or centers. I have observed such waves (after electrical stimulation) spreading both ways along the segments of a recently voided dog's tapeworm, and I have

seen them traveling away from the ridge which forms when one strikes the irritable pectoral muscles of a consumptive; yet in neither of these tissues is there anything corresponding to Auerbach's plexus. Cannon[86] (p. 193) has shown that peristaltic waves continue to travel over the stomach after it has recovered from the making of several cuts through the muscle and plexus down to the mucous membrane; and Meek[316] has made similar observations on the bowel. Apparently when a wave approaches one of the scar tissue barriers it pulls on the muscle on the other side; it stretches that muscle and thereby produces a contraction. Conditions are analogous perhaps to those in Friedländer's[155] (p. 366) experiment in which he cut an earthworm in two and tied the pieces together with a bit of thread. The hind end crawled in coordination with the front end because the pull on the skin was a sufficient stimulus for the underlying muscles.

There is yet another way in which waves may spread from fiber to fiber or across connective tissue barriers, and that is by means of the *electric action-currents*. It is well known that when a muscle contracts or a nerve conducts a small and transitory current is formed. This always runs in a circuit from the active place through the tissue to the resting place and back again through the surrounding medium. It has long been suspected that these action currents might lead to a progression of activity by stimulating the tissue just beyond the active place; and in recent years, largely through the efforts of R. S. Lillie, that view has become strengthened almost to a certainty. Two of his interesting observations are worth quoting at this point. In the ctenophores, there are rows of swimming plates or large cilia which beat in order, so that waves of movement run from one end to the other. If one of these rows is cut off and left for a while in

sea water, it curls up so that the two ends are brought within a few millimeters of each other. It frequently happens then that the wave of ciliary motion jumps the gap between the ends and goes on, so that a wave of activity runs around the ring for hours at a time. Similarly, if a large number of spermatozoa of the annelid Nereis are allowed to stand in a watch crystal they tend to form layers and to contract rhythmically in unison. With the waves of activity going back and forth they give the picture of a layer of ciliated epithelium (Lillie,[266] p. 428). In these two experiments there can be little question as to the mode of transmission across the liquid medium; and certainly nerves have nothing to do with it. Again I find myself emphasizing the independence of the muscle as regards nervous assistance, not because I think the nerves are without function, but because I wish my readers to pay more attention to the graded peculiarities of the muscle and to the workings of ordinary physical laws.

Returning again to the simile of waves spreading in water, it seems to me that some tubular organs may be likened to ponds which are level to begin with; others are more like rivers which have definitely established gradients. In the first case, the waves spread equally well in all directions; in the second, the waves spread more easily downstream than up. Perhaps I can illustrate this point best by showing the evolution of the fixed *gradient in the heart.* As is well known, in that organ the beat follows a gradient of rhythmicity from the sinus to the ventricle. It was Gaskell[158] who first pointed out that "the rhythmical power of each segment of the heart varies inversely as its distance from the sinus." Thus, if we cut a heart into three or four pieces, the one containing the mouths of the great veins will show the greatest tendency to beat rhythmically, and it will have

the fastest rate; the ventricle will be slow to start beating and it will have a slow rate. If, however, we turn to the primitive heart of the sea slug, aplysia, we find a tube which apparently has no constant gradient in either direction. Its beat arises now on one side and now on the other, depending on where the blood produces the greatest tension (Straub,[415] p. 518). Hunter[195] could find no sign of a gradient in the heart of one of the ascidians. In these animals the beat runs for a while towards the viscera and then for a while towards the gills. The pace-making end seems to get fatigued; its rate is slowed and finally the other end is able to assume the pace for a while. A constant direction of contraction may be maintained by electrical stimulation of either end of such a heart (Bancroft and Esterly[29]). It seems to me that Hecht's[181] studies on Ascidia atra show us the very beginning of the fixed gradient which we find in the hearts of the higher animals. He found that although the heart of the ascidian reverses its beat from time to time, the sum of the advisceral beats is about twice that of the abvisceral. Moreover, as we should expect, if the gradient is a little better in the advisceral direction, the rate of conduction is definitely faster in that direction than in the other. If a wave is started in the middle of the heart, going both ways, it tends to efface the abvisceral waves, which according to our theory would have the smaller momentum. It is interesting also that under slightly adverse conditions, as after warming the water, or after diluting or concentrating it, it is the abvisceral beat which is suppressed. We find a little more stable, but still reversible heart beat in the sharks and rays (Bottazzi,[69] p. 372; Gaskell,[159] p. 184). In them the slightest stimulus to the bulbus aortae will reverse the beat and the same stimulus to the sinus will restore it. Even in the higher vertebrates the heart beat can be reversed temporarily by

agencies which lower the rhythmicity of the auricle or raise that of the ventricle (Eyster and Meek[146]). Ordinarily, however, as we have seen, the beat arises in the sinus region and keeps coming from there because that area has the greatest rhythmicity and the fastest inherent rate.

GRADIENTS IN OTHER ORGANS. There is considerable evidence now that peristalsis in the ureter follows a gradient of rhythmicity from the kidney to the bladder (Penfield,[358] Lucas,[275] Sokoloff and Luchsinger,[405] Satani,[383] Wislocki and O'Connor[449]). I have done considerable work with excised segments of ureter and have found that the rate of rhythmic contraction is often fastest in the piece removed from the kidney end. This gradient is not so constant or so marked as it is in the bowel. I have other records from segments of Fallopian tubes and vas deferens which suggest strongly that there are similar rhythmic gradients in those tubes. We may perhaps later be able to state it as a general physiologic law that the direction of transport of material in a tubular organ depends upon gradients of rhythmicity, tone and irritability. When we come to think of it, our experience with engineering and physics should have led us long ago to look for gradients in these muscular tubes. We know that water in a pipe follows gradients of gravity or of pumping pressure; electricity flows along gradients of electro-motive force, the winds follow gradients of barometric pressure, etc. Moreover, anyone who has ever tried to milk a cow knows that it is not hard squeezing which brings results, but a coordinated, graded contraction beginning at the top of the teat and working down to the end.

GRADIENT IN THE INTESTINE. What evidence have we now that there is a gradient in the gastro-intestinal tract?

So far as rhythmicity goes the evidence is overwhelming. It is a simple thing to open an animal under salt solution and to demonstrate that the rate of rhythmic contraction varies from about twenty per minute in the duodenum to ten per minute in the lower ileum (Alvarez,[3] Fig. 3). It is easy also to cut out short segments of the bowel and to show that their rate of rhythmic contraction continues to vary inversely as the distance from the pylorus (Alvarez,[2] and,[10] Fig. 5). A similar gradient can be shown in strips of muscle excised from the wall of the stomach (Alvarez,[5] Fig. 10). There the fastest rate is found in the strip from the lesser curvature near the cardia. It is harder to show the gradient in the colon (Alvarez and Starkweather[17]) but that was to be expected when we remember that the large bowel is more sluggish than the small; it lets the contents lie in one place for long periods of time and it often shows reverse peristalsis. Hence it is that the excised piece is slow to start beating; its rate is slow; it tends to contract down into a hard knot and stay that way, and the gradient is poor and often reversed. In the small intestine of the rabbit and white rat the rhythmic gradient is so fixed and so intimately "built into" the structure of the intestine that one can determine the oral and aboral ends of short excised segments by counting the rates at the two ends.

Reversal Experiments. It has always seemed to me that the gradient is more stable in the rabbit, guinea pig and rat than in the cat and dog, perhaps because the first three have long thin intestines and bulky food, while the last two have short, strong-walled ones and more concentrated food. As will be seen shortly, the gradient must be well established if rough solid particles of food are to be passed on. If we think of the bowel as a pipe line, with uphill stretches in it, we know that water can be forced

through such stretches, but not rocks. Similarly, if we take dogs, cut out sections of their small intestines, turn them end for end and anastomose them again, we can keep the animals alive for months if the greatest care is taken

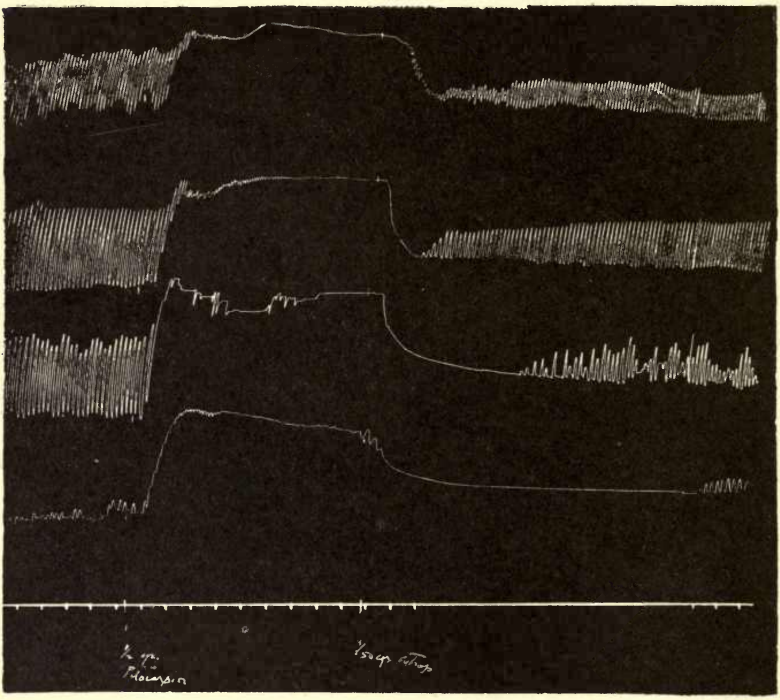

FIG. 5.—To show the difference in the rate of rhythmic contraction in the excised segments. Note also the graded recovery from pilocarpin after adding atropin. From above downward, the records are from duodenum, upper ileum, lower ileum and colon. Time record represents thirty seconds.

to keep rough and indigestible foods from them. Eventually they die from intestinal obstruction, and autopsy shows that bits of straw, bone, wood, etc., have accumulated

at the upper suture and have finally blocked the lumen (Kirstein,[237] Mall,[299] p. 93; Kelling,[233] Mühsam,[331] Enderlen and Hess,[139] Prutz and Ellinger,[365] and [366]; Beer and Eggers,[44] McClure and Derge,[312] Cannon,[86] p. 142). (Fig. 6.) It is clear that the original direction of peristalsis remains fixed in these loops and that liquids can be forced through when solids cannot. Liquids can be pumped into a normal cat's rectum until they flow from her mouth (Senn,[396] p. 221), but Bayliss and Starling[39] (p. 106) found that any attempt to force a solid body like a tampon on a stick in the orad direction through a loop of living bowel was likely to result in severe trauma on account of the great resistance exerted by the muscle. These experiments make me feel that the gradient must be basic and not the result of functional adaptation as some might think. Further evidence for that conclusion is found in the fact that the gradient is just as marked in the fetal intestine, which has not yet functioned, as in the adult animal (Alvarez and Starkweather[11]).

The permanence of the gradient in the gut is to be expected from studies on the lower forms of life. The mouth of a frog is lined by epithelium covered with little cilia which wave in one direction. If a piece of this epithelium is cut out, turned through an angle of 180°, and grafted back again, the cilia continue to beat in their original direction, now contrary to that in the rest of the mouth (von Brucke[75]). In some of the worms the so-called "polarization" is so perfect that if the animal is cut into many small pieces they will all crawl in the same direction towards the point where the head used to be (Carlson,[94] p. 284; Biedermann,[59] p. 288). The early development and stability of these gradients of growth and activity are well shown by some experiments resembling those in which the

segments of intestine were reversed. Hooker[193] chiseled out little segments from the cervical region of the growing spinal cord of frog embryos; he turned these pieces end for end, and grafted them back into place. The interesting

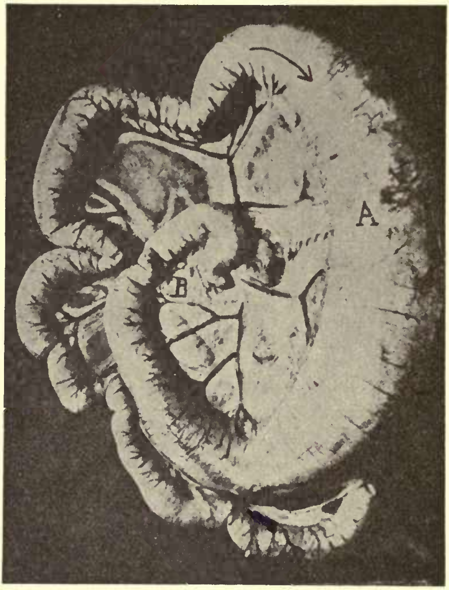

FIG. 6.—Shows the results of reversing a segment of dog's intestine. Note enormous spindle-shaped dilatation on either side of the upper anastomosis. *A*. The point of greatest dilatation is 3 cm. above the suture on the normally directed intestine. Lower anastomosis of reversed loop at *B*, where lumen remains of normal size. (*From McClure and Derge.*)

thing is that the nerve fibers in the reverse segment continued to grow in the original direction in spite of the great force which was exerted against them by the growth of fibers coming down from above. A similar reversal of segments from the duodenal region of tadpoles produces situs inversus in the abdominal organs (Pressler[364]).

To sum up: waves tend to spread out in both directions from a stimulated place on a muscular tube, as ripples spread in a pond when a stone is thrown in. If the stone is thrown into a river the waves will travel downstream more easily than up. Similarly in the heart and intestine, a gradation in rhythmicity makes it easier for the waves to go in one direction than in the other. Actually, in the bowel Miss Starkweather and I found that the effect of a stimulus could be detected much farther caudad than cephalad.[18]

A Gradient of Force. Several years ago while working with a man who had a jejunal fistula I found a marked difference in the *pulling force* exerted by different parts of the bowel on balloons. The jejunum pulled almost constantly and with considerable strength, while the ileum pulled intermittently and weakly. Searching through the literature I found that Hess[187] had observed the same thing in dogs with gastric fistulae through which he could insert balloons into the duodenum. Eighteen centimeters from the pylorus the pull corresponded to 228 grm.; 20 cm. farther down it was 90 grm.; and 12 cm. farther below that, it was 75 grm. Later, Brandl and Tappeiner[72] worked out the rest of the gradient farther down the ileum. It is clear from these experiments that there is a gradient of propulsive force along the bowel much like that in a pipe line.

CHAPTER VI

THE UNDERLYING BASIS OF THE RHYTHMIC GRADIENT

WE have seen that there is a rhythmic gradient in the bowel from the pylorus to the colon. The next question is: What is there underlying this gradient; how did it come, and how is it kept up? Should we not expect to find *anatomic* and *metabolic* gradients running parallel to the rhythmic one? Those who are partial to theories of neurogenic origin will probably think first of looking for some graded difference in the structure of Auerbach's plexus; and actually such a difference has been found. Gerlach[164] showed years ago that the mesh of the plexus becomes coarser and the ganglion cells fewer as one goes from the duodenum to the ileum; and more recently, Kuntz[245] has found a gradient in the concentration of the sympathetic neurones, from the duodenum to a point about 12 cm. above the ileocecal sphincter. It seems to me, however, that as the evidence summarized in Chapter II points to the myogenic origin of the rhythmic movements, we must not rest satisfied with these findings but must look also for graded differences in the structure and chemical activity of the muscle.

Now, it has been shown that the rate of rhythmic contraction of a muscle is dependent upon the rate at which its *chemical processes* go on. Some substance seems to be built up to a certain point and then perhaps exploded or torn down to produce the contraction; if the metabolic rate is

slow it should take longer to complete the cycle. As Woodworth[451] says, the rate of contraction seems to be adapted to the metabolism of a muscle; "if the pause preceding . . . is too short, the contraction suffers from lack of recuperation. If it is too long, the contraction suffers from what we may perhaps call a sort of drowsiness." We know also that warming hastens chemical processes, and Magnus[289] and Taylor and Alvarez[424] have shown that warming the intestine hastens the rate of rhythmic contraction. As we can take a piece of ileum beating 10 times a minute and by warming it, speed up its metabolism so that it will beat 17 times a minute, it seems to me that the duodenum which normally beats 17 times a minute probably has a faster metabolic rate than the ileum.

The warming not only increases the rate of contraction, but it shortens the latent period and markedly alters the form of the contraction curve. These changes probably account for de Zilwa's[454] finding that with a muscle at 40° C. stimuli have to follow each other at intervals of from four to ten seconds if summation is to be obtained. At 25° C. the interval can be twenty seconds or more. Similarly Engelmann[140] while studying the ureter of the rabbit, found that a series of subliminal stimuli might bring about a contraction if the interval between them was not too great for summation. When the irritability was high and the waves were traveling rapidly down the ureter, the interval had to be shorter. It had to be shorter also when using the ureter of the rat, as there the rate of the waves is normally faster than in the rabbit. It seems pretty clear, then, that a muscle which beats at 17 per minute is different from that which beats at 10 per minute. It apparently has been constructed differently in some way, so that its chemical processes will go on at a faster rate, much as those of a baby go on faster than those of

an adult. Those who would like to learn more about this relation between activity and metabolic rate should turn to an interesting article by Miss Hyman.[210] As she (Hyman,[207] p. 378) points out, the word *metabolism* is generally taken to signify the sum of all the energy-producing and substance-producing processes occurring in the body; but as the oxidative processes are the most important ones it is sufficient for our purposes to measure the rate of respiratory exchange. Child[113] (p. 152) uses the word *metabolic* gradient, not because he is satisfied that it is purely or primarily metabolic in character, but because oxidation seems to be the "fundamental factor in life and the chief source of the energy of living organisms . . . Protoplasm is a system in which the chemical reactions of metabolism are so intimately associated with other factors, *e.g.*, colloid dispersion, active mass of enzymes, permeability of limiting surfaces, electrolyte and water content, etc., that to attempt to distinguish one particular factor . . . as primary is at present impossible. The term 'metabolic gradient' . . . means only that the metabolic factor is a characteristic feature. . . . The term 'physiologic gradient' which avoids all specific implications might be substituted for it."

Reasoning along these lines, Miss Starkweather and I[11] measured the CO_2 production of equal weights of muscle from different parts of the bowel and found a definite gradation from the duodenum to the colon. This was true not only for the active but also for the resting muscle. During the last three years Miss Starkweather, Dr. Taylor and I have been collecting data on the oxygen intake of the muscle from different regions, and, as was to be expected, that appears to be graded as is the CO_2 output.

Graded differences have been found also in the catalase content of equal weights of minced muscle. There are many

reasons for believing that this catalase is involved in some way in the normal oxidative processes of the cell, but just how we do not know. It is very suggestive that there is considerable parallelism between the metabolic rates of many tissues and their catalase contents, but there are

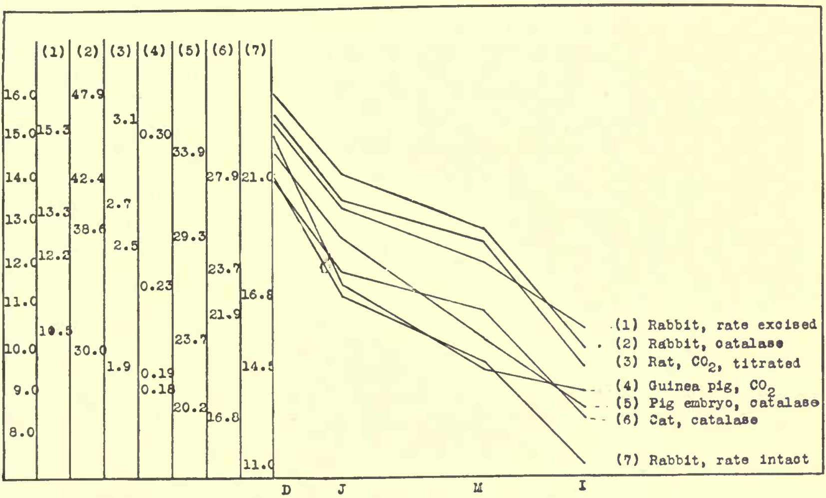

FIG. 7.—Showing the parallelism between the gradients of rhythmic contraction, CO_2 production and catalase content in different animals. In order to bring the different curves closer together, an arbitrary set of ordinates was chosen running from 8 to 16. The seven sets of data were then multiplied or divided by factors which would place the first figure for the duodenum between 14 and 16. The original data are shown as ordinates in the seven columns on the left. The numbered columns correspond to the numbered legends identifying the different curves. The abscissæ represent the four segments along the gut.

exceptions and many possibilities of error; and the subject is still under active discussion. Under the circumstances it can be regarded only as highly suggestive that there is a remarkable parallelism between the CO_2 output and the catalase content of the muscle in the digestive tract. The similarity

of these gradients is shown in Fig. 7. It will be helpful later when we learn more exactly what our data mean, because the technique is easy and the results are generally clear-cut and striking. One thing is certain, and that is that we can show a definite chemical difference between the muscle in the duodenum and that in the ileum or colon. Other forms of chemical analysis would probably show differences in composition similar to those found by Lee, Guenther and Meleney[258] when they compared the diaphragm with other skeletal muscles.

Gradients in metabolic rate have been shown to exist in many parts of the body and it seems to me that their importance in biologic studies is going to be realized more and more as time goes on. They appear at the very *beginning of life* in the ovum and thereafter have much to do in controlling the development of the organism. Thus in the frog, that part of the egg which happens to get the best blood supply from the ovarian membrane forms the embryo (Bellamy[46]). The most rapidly growing part of the embryo forms the nervous system; and the most rapidly growing part of the nervous system becomes the brain. These differences in metabolic rate show themselves as differences in the rate of cell division and in the size of the cells along the future axes of the organism. They are found not only in ova, but in developing seeds, where the polarity is often determined by slight differences in illumination (Child,[113] p. 170).

Once such regions of rapid growth are established, their activity serves to regulate and hold in check the growth of other parts of the developing animal or plant. This control can easily be demonstrated by cutting off or impairing the growth of the tip of an evergreen tree, or the head of a primitive type of animal like a hydroid or a planarian worm. In the simplest organisms there is only the apico-basal

pattern with its corresponding gradient, but in higher forms with lateral symmetry there are radial gradients running at right angles to the longitudinal or polar ones (Child[113]). Thus in certain algae and in trees there is a metabolic gradient along the main trunk from the rapidly growing tip to the roots and there are other gradients in the branches from the tips to the trunk. It is a remarkable thing that in some plants and lower animals these original gradients can be effaced, altered or reversed either accidentally or experimentally: and with the change in gradient goes a change in the structure of the animal. Thus a piece of a planarian worm may develop a new head where the tail used to be; or the experimental obliteration of the polar gradient may cause the new individual to develop along the original lateral symmetry gradient, with a head on one side and a tail on the other. Just as slight accidental advantages in oxygen supply, illumination, or other conditions which favor growth determine the location of the animal pole of the egg, so they may enable some group of cells to seize control and to rearrange an adult organism along new axes (Child,[113] pp. 158, 172).

Although there is still considerable doubt as to the exact mechanism of this control, more and more evidence is accumulating to show the importance of the minute *electric currents* which are produced in these metabolic gradients. If we put two pieces of metal of different composition into a solution of some electrolyte and connect them to a galvanometer, we find a current flowing between them. If the electrodes are chemically the same but the concentration of the electrolyte about them varies, a current will again be set up. In the tissue there are no metal electrodes and no wires; but differences in ionic concentration on the two sides of cell membranes and

differences in the rates of oxidation along growing axes give rise to circuits through the tissues themselves (Lillie[267]). If two regions with different oxidative rates are connected through wires to a galvanometer, the more actively growing or more motile one is always electro-negative to the other; that is, the current flows towards it in the wire. In the tissue, of course, the current flows from the more active end of the metabolic gradient to the lower. Similarly, in a battery, the zinc *plate* is positive to the copper, although the copper *terminal* is positive through the galvanometer to the zinc terminal. Years ago Hermann[185] noticed that the growing root tips of seedlings were negative to other parts of the root. Müller-Hettlingen[337] confirmed this and showed, moreover, that the growing tip of the plant was negative to all other regions. Later, in 1902, Mathews[301] found that the head of a polyp was electro-negative to the stem, and anterior levels of the stem negative to posterior ones; and in recent years Child and his students have found gradients of electric potential along all the axiate animals and plants which they have studied (Child[113]).

We are just beginning to see that these minute differences in electric potential can play a large part in the development and life of the organism. They not only bring about certain chemical reactions which otherwise would not take place, but they direct them along certain lines. One of the simplest and best known examples of the "chemical action at a distance" is found in the electric battery where two pieces of zinc and copper form the electrodes and dilute sulphuric acid serves as the electrolyte. Very little chemical action takes place until the two pieces of metal are connected by a wire, but immediately after that the zinc begins to be eaten away. Many other interesting examples of this action might be supplied, and if space permitted I might review the work of Lillie[267]

and others who have used weak electric currents to build beautiful structures closely resembling corals, seaweeds, trees, toadstools, etc. Nineteen years ago Mathews[301] suggested that we might be able to modify and control at will the regeneration of lost parts in lower animals by modifying the bio-electric currents, and recently Lund[282] and Ingvar[211]

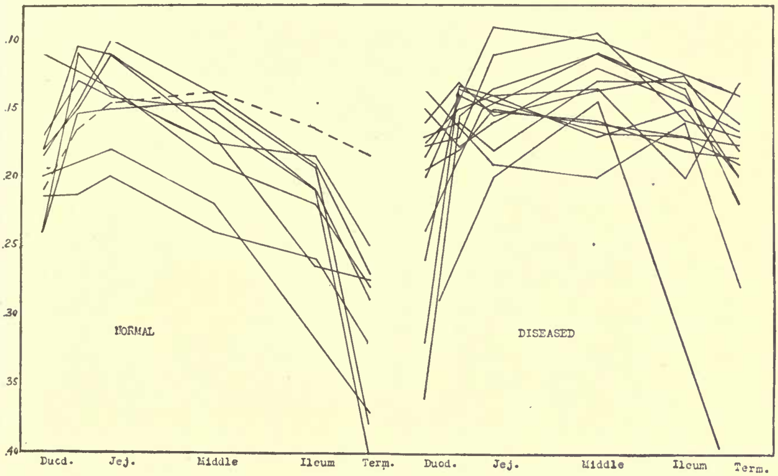

FIG. 8.—Shows gradation in the latent period of the dog's small intestine. The ordinates represent parts of a second; the abscissæ, distances from the pylorus. The data shown at the right were secured from distempered or otherwise diseased dogs.

have shown that such control is possible. Lund was able to determine the point of regeneration in Obelia; and Ingvar caused the cell bundles in tissue cultures to grow along the lines of force produced electrically in his tissue cultures. He found, moreover, that he could produce these effects with currents comparable in intensity with those found in living tissues.

In addition to the axial gradients of growth there are

other metabolic gradients in various organs. As was to be expected from the character of the electrical phenomena, there is a gradient in the embryonic heart of the chick from the sinus to the ventricle (Child,[113] p. 169). MacArthur and Jones[288] found a gradation in respiratory rate in the nervous system from the cerebrum to the peripheral nerves, and Tashiro[422] has demonstrated gradients of CO_2 production along nerves. He believes that these gradients which are from the center to the periphery in motor roots and from the periphery to the center in sensory roots have something to do with the conduction of impulses.

This long digression into fields distant from that of the intestine has been made in order to show the growing importance of the gradient idea in biology. It will undoubtedly be a long time before research workers are in agreement as to the exact significance of these gradients, but, as Child says, there can be no doubt as to their existence. They are there, and the natural inference is that they must be useful or at least, worth studying.

Chapter VII

OTHER RELATED GRADIENTS

LATENT PERIOD. When a muscle is stimulated it does not respond immediately. There is a short, so-called latent period the length of which depends largely on the metabolic rate of the muscle. As the metabolic rate has been shown to vary in different parts of the gut, we would expect the latent period to vary, and actually it can be shown that it does. As will be seen in the next chapter, it is quite easy to show a gradient of latent period in the stomach. In the bowel the technical difficulties are much greater, and it is almost impossible to get satisfactory measurements with some animals. In many others, however, I have been able to show a definite gradation from a short latent period in the lower duodenum or upper jejunum to a long one in the ileum. Figure 8 shows how the data run in dogs. The first portion of the duodenum generally reacted poorly and after a fairly long latent period. That may be due at least in part to its relatively greater susceptibility to the trauma of excision and handling. While studying these latent periods and the shapes of the contraction curves, I could not help being greatly impressed with the marked differences which exist between the muscle in different parts of the stomach, small bowel and colon.

Tone. When a piece of duodenum or jejunum is cut out it tends to contract down to perhaps half of its original length and the ends roll over so as to form little cuffs.

A piece of ileum may even lengthen a little, and its cuffs, if any form at all, are narrow as compared with those of the upper bowel. I found recently that these little cuffs with their differences in width were described in 1902 by a medical student (Wolff[450]). Similar differences in the tone of the muscle from different parts of the stomach are described in the next chapter. When a loop of bowel is full of food and actively segmenting it is generally contracted tonically. Later, when it empties, it may relax and more than double in length (Alvarez,[3] Mall,[298] p. 451). These permanent and transitory differences in tone are undoubtedly of great importance in digestion, and should be studied further. As Cannon[84] (p. 27), also[86] (p. 195), and[88] (p. 242), and[87] (p. 417), has shown, they have much to do with initiating and regulating peristalsis in all parts of the digestive tract. He was able to reverse the direction of peristalsis in a loop of intestine by dipping the caudad end into a weak solution of $BaCl_2$ (Cannon,[90] p. 119). As is well known, that raises the tone of the muscle. In the crop of the sea slug (von Brucke[75]) and in the earthworm (Biedermann,[59] p. 483) it has been shown that the contractions start from the place of greatest tension. Changing that, the direction of peristalsis can be reversed at will. Trendelenburg[431] has observed the tendency of a loop of guinea pig intestine to contract more at the cephalad end than at the caudad, and has suggested that this gradient of tone accounts for the direction of peristalsis.

Rhythmic Tendency. When a number of segments from different parts of the rabbit's intestine are placed in a beaker of warm oxygenated Locke's solution, the duodenal segment is generally the first to begin beating, and the colon is generally the last. Figure 5 shows also that when a number of beating segments are thrown into spasm by pilocarpin

and then released again by atropin, there may be a remarkable gradation shown in the tendency to resume rhythmic activity. Conditions in the intestine are very similar, therefore, to those in the heart where the excised auricle can be made to beat easily, but the ventricle only with difficulty. If this tendency is as marked in the intact animal as it is in the excised segments, its usefulness is obvious. It will conduce to the starting up of normally directed peristalsis after the bowel has been paralyzed by poisons or by powerful splanchnic inhibition.

Irritability. As stated in the preface, the first gradient which I noticed was one of irritability. I found that the duodenum was more responsive to distention by gases or food than was the ileum. Later, while working on men and women with intestinal fistulae I found that a balloon in the jejunum was kneaded and pulled on almost incessantly; in the ileum, it was often left undisturbed for a half hour or more, and in the colon it was left entirely alone except for an occasional contraction immediately after it was distended. A search through the literature showed that others have made similar observations. Van Braam Houckgeest,[194] Floel,[153] Schillbach[386] (p. 281), Bokai,[61] Biedermann[56] (pp. 372 and 379), Lüderitz[278] and,[279] and Bayliss and Starling,[39] all comment on the greater activity and responsiveness of the duodenum and jejunum: and the last named writers thought that "ascending augmentor stimuli" and the "higher excitability of the duodenal end of the gut" might perhaps have something to do with the preponderance of downward peristalsis. Schillbach used faradic stimuli so weak that they had practically no effect on the bowel except in the upper jejunum and upper end of the colon. Similar results were obtained by Biedermann with the galvanic current.

He thought the irritability was graded downwards and that there must be a histologic gradient perhaps in the structure of Auerbach's plexus. He tried to prove this pharmacologically much as I tried in 1913.

It is easy to show the gradient of irritability in the bowel with distending balloons, pinches, and salt crystals, but it is not easy to show it with the electric current. I have tried many times to work out a satisfactory technique but have never been able to convince myself that the threshold for the duodenum is less than that for the ileum. The rhythmic changes constantly going on in the intestinal muscle and the prolonged refractory periods make such experiments unsatisfactory and inconclusive. There seems little doubt that the chemical threshold is the same in different parts of the gut; that is, five segments from different regions, if they are all beating strongly, will respond equally to minute dosages of drugs like barium chloride or pilocarpin.

Marked differences in irritability were found in different parts of the wall of the stomach, but those will be discussed in the next chapter.

Early Observations on the Rhythmic Gradient. This little book would not be complete without references to the work of previous writers on the subject. When in 1913 I started studying the differences in rhythmic rate which appeared on my tracings from two different parts of the bowel, Dr. Walter B. Cannon told me that he had noticed such differences but he had never had time to analyze them, and so far as he could remember, he had never read anything about them. During the next year a search was made through the literature, and little was found that would lead anyone to suspect that the neuromuscular tube of the small intestine is any different in the duodenum from what it is in the

ileum. Even Roith,[375] who had the vision to see that the peculiarities of colonic activity might be due to regional differences in muscle and tone, states that the small intestine is the same throughout. After long search, however, I found references to differences in rhythmicity in Luciani's "Textbook of Physiology,"[276] and in articles by Legros and Onimus,[259] Lüderitz,[279] and Laqueur.[254] Legros and Onimus thought that the emptiness of the jejunum was probably due to its fast rate. Nothnagel[343] remarked upon the fact that in the rabbit the movements of the upper bowel are stronger and more continuous than those of the lower. Stiles[412] noticed a rhythmic gradient along the esophagus of the frog; and Bottazzi[67] and[68] (p. 341) ascribed the aboral course of the waves in the esophagus of the sea slug Aplysia to the greater tone and excitability of the oral region in which they arise. He suspected a difference in rate, but he could not show it. Bottazzi deserves much credit because he knew what he was looking for, and the value of what he found in the esophagus. I cannot tell from their papers whether the later writers knew of the work of Legros and Onimus. Pohl[361] knew of Lüderitz's work, and Luciani may have derived his knowledge from the same source. As was shown in the preceding section, a number of the older writers observed the gradient in irritability. Hess,[187] and Brandl and Tappeiner[72] noticed the gradient in pushing force down the bowel, described in Chapter V.

Unfortunately, these men did not realize the value of what they had found; they did not have the present day background to fit it into, and they did not keep hammering away on the subject until they compelled their confrères to listen. We may sometimes regret the fact that textbooks are sluggish and conservative things, but when we remember that it often takes from fifty to a hundred years to purge them

of some misquotation or false conclusion, we should perhaps be glad that it takes ordinarily from ten to twenty years of reiteration to get a new idea included. To my mind, the main cause for the slow development of our knowledge of the mechanics of peristalsis is to be found in the fact that most of the men who worked on the bowel were so concerned with problems of nerve supply or drug action that they made mention of important physiological observations only in passing. A striking illustration of this is found in Jacobj's[212] description of reverse peristalsis in the colon. This was buried away and lost in an article on colchicum poisoning until some time after Cannon's independent discovery of the same phenomenon.

Anatomic Differences. The differences in the structure of Auerbach's plexus in different parts of the gut have already been mentioned (Gerlach[164] and Kuntz[245]). The presence of "nodal tissue" at the cardia and ileocecal sphincter will be discussed in Chapter XI. A gradation in the thickness of the muscular coat of the small intestine from the duodenum to a point a little way above the ileocecal sphincter has been described by a number of anatomists (Tourneux and Hermann,[429] Flint,[152] Merkel,[319] Jonnesco,[219] Kölliker,[240] Monks[323] and,[324] Schäfer[384] (pp. 536 and 552); Todd[427] (p. 145). Unfortunately, the normal transient differences in tone and the uncertain effects of the fixing agents make it hard to get trustworthy figures. These difficulties and the ways of meeting them are discussed in Rost's[378] article on the differences in the thickness and tone of the muscular wall in the colon of man.

One of the most interesting graded differences is the one pointed out so clearly by Monks.[323,324] He calls attention to the fact that there is a progressive decrease in the vascu-

larity of the mesentery from the duodenum to the ileum. (See also Latarjet and Forgeot[255]). Part of this difference in the mesenterial arches is due to the greater functional activity of the mucous membrane in the jejunum, but part of it is due undoubtedly to the greater activity of the muscle there. These observations fit in with those of Krogh,[244] who has shown that the blood supply to a muscle is an accurate index of its metabolic rate. In keeping with its sluggishness and its slow metabolic rate, the colon has a relatively poor blood supply; so poor that surgeons have to be very careful when making anastomoses not to impair it further (Okinczyc[344]).

Chapter VIII

GRADED DIFFERENCES IN THE STOMACH WALL

When it was seen that the rate of rhythmic contraction in the small intestine varies inversely as the distance from the pylorus, the next question was: How about the other parts of the digestive tract? Could the *primitive digestive tube* have been constructed originally so that the rate would be highest at the pharynx and lowest at the anus? Although this question cannot be answered conclusively as yet, there is considerable evidence in favor of the view that the whole tract once showed such a gradation (Alvarez[5]). Thus, the rates of contraction in different parts of the colon of the rabbit and cat fit quite well into a prolongation of the curve plotted from the rates in different parts of the small bowel. These rates vary in the rabbit from 6 to 10 per minute near the cecum to from 3 to 5 per minute near the anus.

It is impossible to say much about the esophagus in mammals because in them that tube is made up almost entirely of striated muscle; and the smooth fibers appear only in the lower third or fourth. Longitudinal segments from the lower end of the esophagus of laboratory animals show a high rhythmicity when placed in oxygenated Locke's solution. The fastest rate observed in the cat was 14 per minute and in the rabbit 19 per minute. As we should expect if my hypothesis is correct, these rates are higher than those for the excised duodenal segments in these animals. In the frog's esophagus, where the muscle is all of

the smooth variety, we can see that the rate of rhythmic contraction varies inversely as the distance from the pharynx. I have shown these differences also in the esophagus of a snake. In the frog the esophageal rate was generally faster than that of any other part of the digestive tract.

Even if further work on animals should show definitely a gradation of rhythmic activity from pharynx to anus, we should still have to explain the low rate of the gastric waves in mammals:—from 3 to 4 per minute in the rabbit, dog and man, and from 4 to 6 per minute in the cat. A possible way out of this difficulty is suggested by the literature on another muscular tube—the heart. Gaskell[159] looked on that organ as an elaboration of a simple tube which has become twisted on itself and has bulged in places. There the muscle has become specialized so that it can contract and empty its cavities more quickly. Gaskell felt that the "development of this nearer approach to striated muscle is made at the expense of the original rhythmical power."

The Primitive Digestive Tube and Its Modifications. A glance at Figure 9 will show how the stomach also has been evolved from a simple tube, first by an enlargement; secondly, by a bending of the pylorus towards the cardia; and thirdly, by the addition of one or more cecal pouches. The stomach of the eel consists almost entirely of such a pouch which has grown from the convex side of a bend in the original tube. It is very obvious in such a stomach that the primitive tube is to be found along the lesser curvature. Even the complicated stomachs of ruminants can be resolved into a series of ceca arranged along the original tube (Oppel,[346] Huntington[196]). The fundus of the human stomach represents such a cecum which very early in life grows out from the greater curvature (Keith and Jones,[232] Lewis,[262] p. 500). Lewis shows

that in a 10 mm. human embryo, the stomach is made up of three parts: The expanded, conical lower end of the esophagus; the long tubular antrum, a little wider than the adjacent duodenum; and a small fundus. The end of the esophagus meets the pyloric antrum at the incisura angularis.

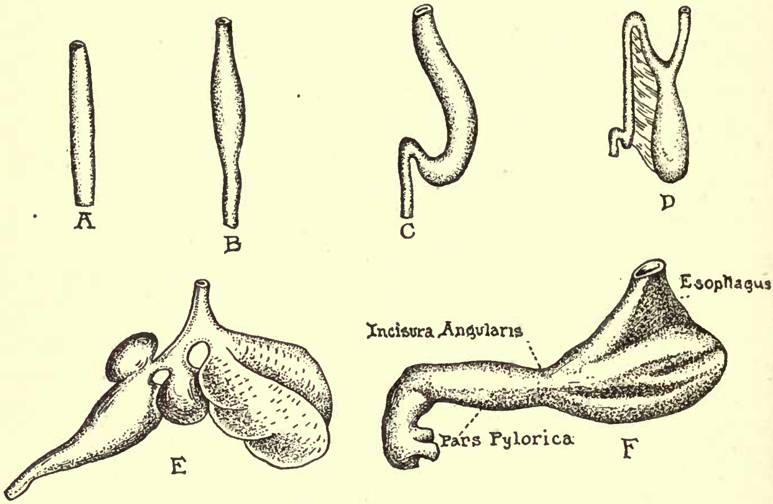

FIG. 9.—Shows the development of the stomach. (*a*) Stomach of the pickerel (Nuhn); (*b*) stomach of Proteus anguineus (Nuhn); (*c*) stomach of Scincus ocellatus (Nuhn); (*d*) stomach of the eel (Huntington); (*e*) scheme of the ruminant compound stomach (Nuhn); (*f*) stomach of a 10 mm. human embryo (Lewis).

Later the fundus grows at the expense of the other two parts so that in the adult the end of the esophagus is represented only by the cardiac antrum and that prolongation along the lesser curvature which forms the gastric canal. Thus in the adult, the pyloric antrum makes up a much smaller part of the stomach than it did originally (Fig. 9 F).

The primitive tube must accordingly be looked for along the lesser curvature. It is suggestive that this part of the stomach is lined by an epithelium differentiated least of all from that of the intestine; that is, the glands are mainly of the pyloric type (Bensley,[47] Lansdown and Williamson[252]). A similar arrangement is found in most of the domestic

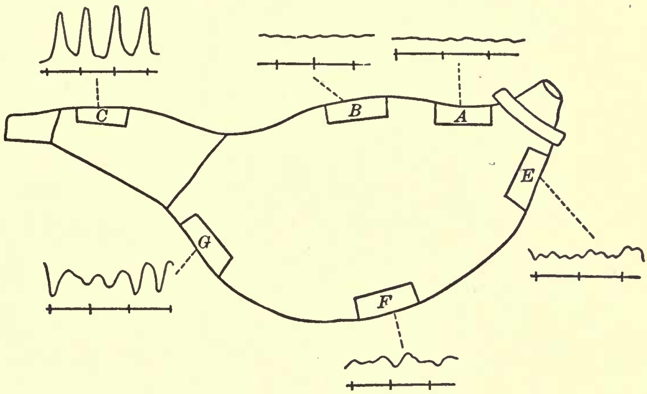

FIG. 10.—A diagram of the cat's stomach to show the location of the principal strips studied and the types of tracing peculiar to the different regions. The time tracing represents thirty-second intervals.

animals (Haane[175]). It is interesting also that many animals, including man, have a loop of muscle fibers along the lesser curvature which on contracting make a gutter, or in the ruminants and kangaroos an actual tube which conducts fluids from the cardia to the pylorus. In this way the primitive tube is largely restored; and food is prevented from entering the cecal parts of the stomach. This tube is called the canalis gastricus (Jefferson[214]).

If this idea of a pouch evolved from a primitive tube is correct, we should expect to find the most rhythmic tissue on the lesser curvature near the cardia. Actually, we do find it there (Alvarez[5]).

DIFFERENCES IN RHYTHMICITY. Differences in rhythmicity were shown by cutting off little strips of muscle from different parts of the stomach and getting them to contract in warm aerated Locke's solution. The segment from the lesser

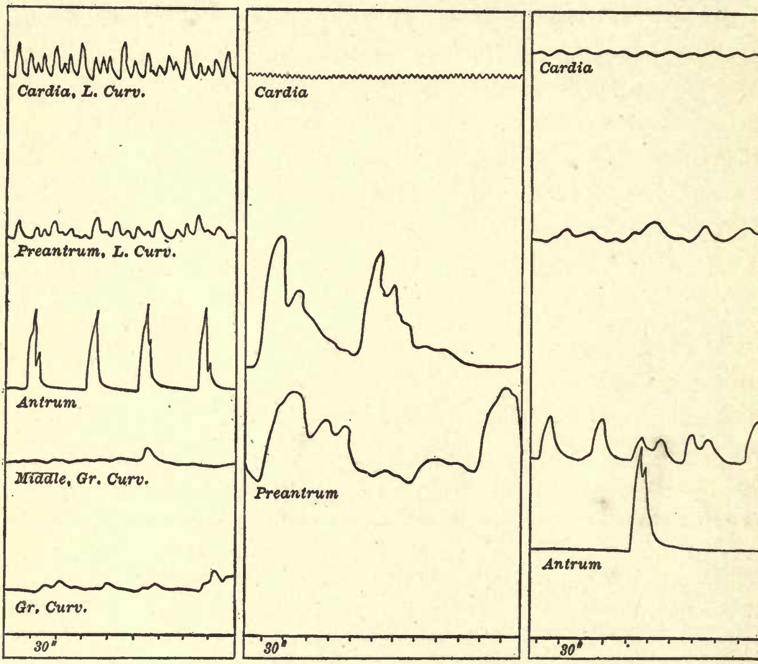

FIG. 11.—Records from five strips from different parts of the dog's stomach; of three strips from the lesser curvature of the human stomach and from four strips from the greater curvature of the human stomach.

curvature next the cardia always showed the greatest tendency to rhythmic contraction. Strips from the greater curvature, and particularly from the pyloric antrum, were slow in starting; and many would not contract at all. The rate varied ordinarily from about 11 at the cardia to

about 2 near the pylorus. In the rabbit, for some unknown reason, the muscle on the greater curvature next to the pyloric antrum sometimes showed a tendency to beat almost as fast as that from near the cardia. Figure 10 shows that there is somewhat of a rhythmic gradient from the cardia to the pylorus. It shows also the marked differences in the shapes and amplitudes of the contractions in the different regions. On the lesser curvature the amplitude is very small, and in the antrum it is large. Figure 11 shows that these differences are just as characteristic in tracings from bits of muscle removed from the human stomach. The peculiar form of the contraction curve exhibited by the muscle in the pyloric antrum was observed even in the frog.

Differences in Tone. Differences in tone were observed while studying the strips of excised muscle. When the pieces were removed on the lesser curvature, not only did they contract markedly, but the edges of the cut retracted so that the piece was several sizes smaller than the hole. On the greater curvature, the piece sometimes stretched a little and became even larger than the hole. The differences in the amplitude of contraction in the different segments may be ascribed partly to these differences in tone and partly to differences in the structure and arrangement of the muscle fibers.

Difference in Irritability and Latent Period. A search of the literature showed that several men have observed local differences in the irritability of the gastric wall. Meltzer,[317] noted that the fundus was rather unresponsive and that the whole stomach was less sensitive than the bowel. Lüderitz,[280] noted that the contraction often appeared

cardially to the stimulated place. He thought that the lesser curvature was more sensitive than any other place. He noted the peculiar type of reaction in the pyloric antrum, and the insensitiveness of the fundus. Ducceschi,[131] studied the irritability of the interior of the stomach. He thought the reactions to mechanical stimuli were quicker and more energetic near the pylorus than anywhere else. The cardia,

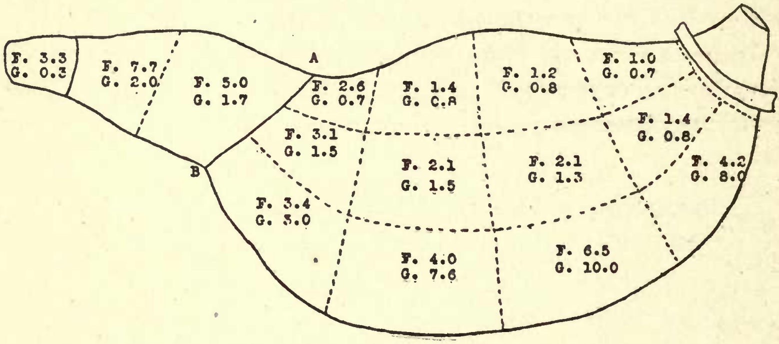

FIG. 12.—Anterior surface of the stomach of the cat, showing the average intent periods after faradic and galvanic stimulation in different regions. The figures indicate seconds. *AB* is the dividing line between the pars pylorica and the body of the stomach. The other unbroken line represents the pylorus.

however, was most responsive to faradic stimulation, and its latent period was shortest. Weak acids also had a more pronounced stimulating effect on the cardia than on the fundus. In the pyloric antrum, the effect was generally reversed, the active movements being inhibited. The presence of a balloon in the antrum almost always gave rise to active peristalsis; but this was not the case in the fundus. Waterston,[440] comments on the local differences in the response of the human stomach to the formalin in embalming fluid.

He thinks the pyloric sphincter and the upper end of the pyloric antrum have the most irritable muscle. Carlson,[95] has noted that the hunger contractions are mainly in the fundus while the digestive contractions are mainly in the pyloric part. "Either these two regions of the stomach react differently to local stimulation of the gastric mucosa or else the nervous mechanisms concerned . . . are different." May,[302] found the inhibitory effect of vagus stimulation more pronounced on the cardia than on the pyloric end of the stomach.

Barbera's work is very important.[30] He found that when the stomach of a frog is stimulated at any point by weak faradic shocks, the contraction appears first at the cardia. He found that this is due to a shorter latent period at the cardia, *i.e.*, 8.4 seconds, as compared with 10.2 seconds in the middle region, and 13.5 seconds near the pylorus. I confirmed this work of Barbera (Alvarez[6]), and showed also that the cardia is the most irritable part of the frog's stomach. Frequently stimulation of the pyloric region brought about contractions near the cardia and in the duodenum before any effect was observed under the electrodes.

Similar work was done on the stomachs, excised and intact, of rabbits, cats and dogs. The more satisfactory work was done on the excised stomachs because the irritability of the stomach in the intact animal, anesthetized, and with the abdomen open, is considerably lower than that of the organ removed from the body and kept warm in a moist chamber.

In the rabbit, the reaction to electrical stimulation near the cardia is almost immediate. This is due largely to the fact that strands of striated muscle extend from the esophagus onto the stomach and 2 cm. beyond the cardiac

thickening. Figure 12 shows that the latent period lengthens as we pass from the cardia to the pylorus and from the lesser to the greater curvature.

The pyloric ring was more irritable, and showed a shorter latent period than did the rest of the antrum. This point should be emphasized, as it may have important clinical bearings. The duodenum, a few millimeters away from the antrum, responded much more promptly to the galvanic current. For some unknown reason, the difference was not so marked with the faradic current. There is a definite gradation in the ratio between the latent periods with the two types of current in different parts of the stomach; but the exact explanation for it will have to await further study.

Some work was done on *human stomachs* excised shortly after death, and *in situ* during abdominal operations, but the results were not very satisfactory. Enough was done to show the differences between the effects of faradic and galvanic stimulation in the antrum, and the differences in irritability between the stomach and duodenum.

Much of the sluggishness of the intact stomach seems to be due to nervous inhibition. If the irritability of the muscle were dependent upon its nervous connections, we should expect the reactions to become progressively slower after removal of the stomach from the animal, and particularly after the trauma of cutting the strips. Yet the opposite is true. The latent period was often shorter, and the rhythmicity in all but the cardiac strip was generally much better on the second or third day than on the first. Good records were secured from bits of muscle removed from the stomach of an executed criminal and kept in Locke's solution at 10°C. for four days.

Differences in Excised Segments. There was a marked difference in the appearance of the contraction curve obtained by stimulating bits of muscle cut from the pyloric antrum and the cardiac region of the frog. The cardiac strips showed by far the greater rhythmicity (Alvarez,[7]). They suffered more from the trauma of excision

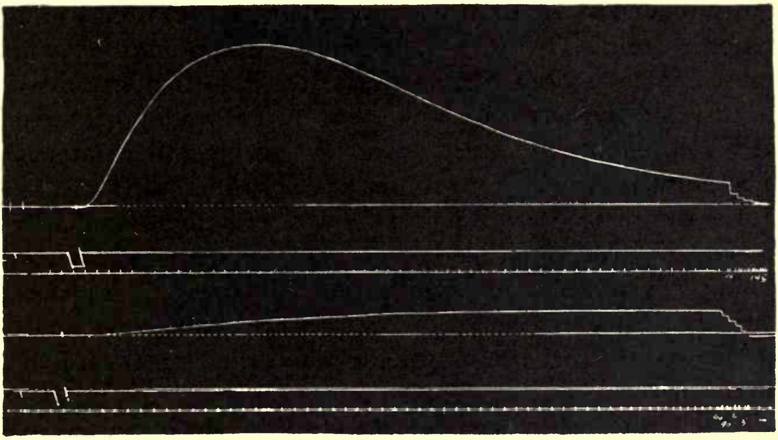

Fig. 13.—Contraction curves from strips from the frog's antrum (upper) and the cardia (lower). The same strength of faradic current was used. Time markings represent seconds. Magnification of lever 4.5 : 21.

and they recovered slowly as compared with the antral strips. They suffered more damage also from strong faradic currents. They did not stand being kept in the ice-box so well as did the strips from the antrum. Strips from the middle of the frog's stomach reacted more like those from the cardia than like those from the antrum. The muscle in the antrum of the frog's stomach is firmer to the touch and there is a marked difference between it and that in the rest of the stomach.

Similar differences were found in the reactions to artificial stimulation of strips of muscle excised from different regions of the stomachs of cats, dogs, and rabbits (Alvarez[8]). Speaking roughly, the latent period varied inversely as the distance from the cardia. The shape of the contraction curve was different and characteristic for the various regions of the stomach. (Fig. 13.) The muscle from the fundus showed a great tendency to remain tonically contracted after stimulation, while the antral muscle relaxed promptly. The muscle in the pyloric antrum seems to be particularly fitted to carry on the active work of the stomach, while the fundus serves to maintain a steady tonic pressure on the contents. The muscle from the antrum has a color different from that in the rest of the stomach. It is redder and tough like that of a gizzard. The muscle from the pacemaking region is soft to the touch like coagulated fibrin. Todd,[427] (p. 95) says the muscular fibers in the pyloric region are bulkier and more separated from each other than in the cardiac portion of the stomach.

When the strips were left for forty-eight hours in the ice-box those from the antrum showed themselves peculiar in that their latent periods were shortened while those of the other strips were more or less lengthened. In diseased animals all but one or two strips generally showed a lessened irritability and a lengthened latent period. In some of these sick animals the latent period of the antral strip was definitely shortened. This lengthening of the latent period at the cardia with a shortening at the pylorus often upset the normal gradient usually found.

Difference in Catalase Content. I have already commented on the gradation in the catalase content of the muscle from the duodenum to the ileum. A similar gradation

was found in the stomach (Alvarez and Starkweather[14]). This gradient was more marked along the lesser curvature than on the greater. In the rabbit the amount of catalase was larger along the lesser curvature than along the greater. For some unknown reason this ratio was reversed in the

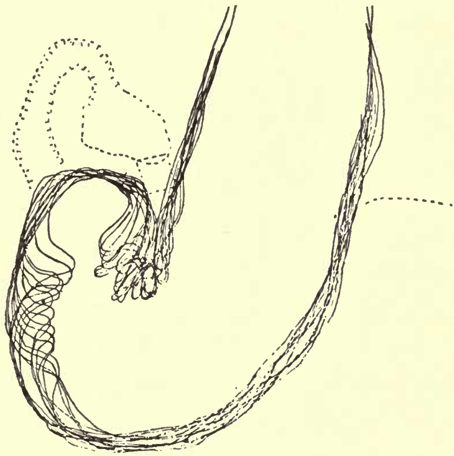

FIG. 14.—Shows the superimposed outlines of a number of gastric radiographs taken cinematographically. Note the small amplitude of contraction in the upper part of the stomach and the change in the character of the waves when they reach the pyloric antrum. (*From Groedel.*)

cat and dog. Further work needs to be done on the metabolism of the muscle in the stomach wall.

DISCUSSION

It has been well established by many workers that the stomach performs its functions after section of the extrinsic nerves (Cannon,[81] p. 429; Rubaschow,[379] Krehl,[241] and even after its removal from the body (Hofmeister and Schütz[191]). We see now that local peculiarities in the muscle, with

graded differences in rhythmicity, irritability, tone and latent period probably have most to do with directing the peristaltic wave as it travels over the stomach. As in the heart, so here, the waves probably have their origin in the most highly rhythmic and sensitive area. We may say perhaps that the region on the lesser curvature next to the cardia is the pacemaker for the stomach. It must be remembered, however, that the activities of the heart and stomach are very different. In one, the impulse travels so rapidly that the organ appears to contract as a unit; in the other a series of waves travel slowly over the sac, gently kneading its contents.

A glance at one of Groedel's illustrations (Fig. 14) made up of the superimposed outlines of a dozen serial radiographs of the same human stomach, will show how little the lesser curvature, as far as the incisura angularis, is affected by the peristaltic waves. The amplitude is very small, just as it is in excised segments of muscle from this region. Appearing at a variable distance from the fundus, the gastric waves seem to travel almost entirely along the greater curvature, getting deeper as they approach the antrum. At that point their character suddenly changes: they involve the whole circumference of the stomach and are so deep that they sometimes meet in the center. It seems to me that these local differences in the shape and depth of the peristaltic wave correspond perfectly to the regional peculiarities of the tone and amplitude of contraction of the muscle fibers through which it must pass. The reader may grasp the idea more easily if he will think of an impulse traveling down a series of strings, the tension of which varies inversely as the distance from the top. At the upper end the waves will have a low amplitude and a high frequency, while at the lower they will have a large amplitude and a low frequency.

It is interesting in this connection that Jenkins and Carlson,[215] say, after studying the muscles of a number of molluscs that "the rates of nervous impulse and forms of the myograms of the three well express the differences in the degree of activity manifested by the three." The squid is the most active simply because it has the most efficient muscles.

In the heart, when the sinus node is damaged, the tissue with the next highest rate assumes the pace. Dittler,[129] noticed a similar shifting in the crop of the sea slug Aplysia; and we know that waves will run aborally over the pyloric portion of the dog's stomach even after it has been separated from the cardiac end (Kirschner and Mangold[236]). There is little interference with peristalsis in the human stomach after so-called sleeve resections of the middle portion (Faulhaber and von Redwitz[148]); and Cannon has shown that waves will keep traveling over the organ quite normally after the healing of several encircling cuts which have been made through the muscle down to the mucosa (Cannon,[89] p. 258).

Rather against the view that the waves originate near the cardia is the common observation that they seem to appear now here, now there on the greater curvature. Cannon[89] (p. 257) felt that the pulsatile source of the gastric wave has no fixed seat. He showed that a wave is likely to appear at the spot where a certain balance is struck between the tone of the muscle and the internal tension. My records from the intact intestine show clearly that a peristaltic rush which apparently has begun in the lower ileum has really come as an unnoticed ripple all the way from the duodenum (Alvarez,[3] p. 273, Fig. 3). I believe that the same thing takes place in the stomach; that is, ripples sent out from the cardia deepen into large waves at

certain points where the conditions of tension are suitable. Carefully made serial plates will show these ripples along the lesser curvature as far up as the cardia. Work now being done in my laboratory shows, moreover, that strong action currents run rhythmically even over stomachs which show absolutely no sign of peristalsis.

One question which may arise is: Why should the rates of the excised strips in the rabbit and dog be so much higher than that of the intact stomach? Only in the cat do they correspond at all. It is different in the intestine where the rates of the intact bowel and of the excised segments agree quite closely. The faster rates in the stomach probably indicate a reserve rhythmicity of which the cardia has the greatest amount. It does not seem likely that the normal slow rate is due to depressor effects from the vagus, as peristalsis is not quickened after double vagotomy (Cannon,[81] p. 432). More probably the longer intervals between beats are needed for adequate rest and recovery so that the muscle can maintain a constant level of efficiency. For the same reason the medusae pulsate normally at only about one-seventh of the rate that they are capable of maintaining under certain conditions (Mayer,[303] p. 379).

Clinical Applications. If these gradients of rhythmicity irritability, latent period, tone, and (probably) metabolism, are helpful in maintaining the normal aboral peristalsis, it is very likely that an upset in them will interfere with the motility of the stomach. We have seen that the muscle at the cardiac end is so much more sensitive to adverse conditions and to toxins that the gradients are found flattened in diseased animals. The gradients may be upset also by ulcers near the pylorus which greatly increase the irritability of that region; and actually, at times, we do see reverse peristalsis in the stomach.

The theory that the gastric waves originate near the cardia is helpful in explaining some of the peculiarities of gastric motility with ulcers, particularly on the lesser curvature. Ordinarily a wave originating at the cardia has to travel a little faster along the greater curvature than along the shorter lesser curvature if the two ends are to reach the pylorus at the same time. Not infrequently a small ulcer on the lesser curvature calls attention to itself by altering the rate of conduction so that the two ends of the wave do not reach the pylorus simultaneously. The resulting distortion in that region is easily recognized by the expert. Often in these cases the stomach does not empty on time, although it can easily be seen that the pylorus is patulous. Sometimes the arrival of part of the wave at the pylorus seems to block the other part of it still advancing along the other curvature. It seems to me probable that such differences in conduction would be still more exaggerated after operations which shorten the lesser curvature. A number of surgeons have actually found that a *V-shaped excision* for ulcer on the lesser curvature must not be done, because it leaves a stomach that does not empty properly (Mayo,[305] Stewart and Barber[410]). If any tissue is to be removed from one curvature, a similar amount must be removed from the other, and the so-called sleeve resection leaves a stomach which functions quite normally. Theoretically the sleeve should be a little wider on the greater curvature than on the lesser.

While watching gastric peristalsis in the rabbit and also in man it has often seemed to me that there must be a wave of excitation traveling ahead of the visible contraction. Owing to its greater irritability and shorter latent period, the pyloric ring can respond to this excitation a little ahead of time, and in doing so, it blocks the advancing peristaltic

wave and keeps that from putting any pressure on the sphincter. Time and again in cats I have watched a similar mechanism protecting the ileocecal ring against undue pressure from the colonic side. It contracts firmly in the face of the advancing colonic waves (reverse peristalsis) and blocks them before they can force material past the sphincter. Similarly, the sacculus rotundus in the rabbit protects the ileocecal sphincter from too much force from above. It has been shown in some of the lower forms of life that intestinal material does not press up to, and pack against the sphincters. The real barrier is not the valve but a ring of muscle with high tone and rhythmicity placed around or just above it (Bottazzi[67] von Brücke[74]). This not only blocks approaching waves but starts up reverse ones, which save the sphincter from being put under pressure. These observations must be thought of when we find a large six-hour residue in the stomach, good peristalsis and an open pylorus.

It is well known that the pyloric sphincter sometimes shows considerable spasm even when the lesion causing this spasm is well up on the stomach or down in the bowel. This might be explained as being due to the greater irritability of the sphincter as compared with the surrounding muscle. Having a lower threshold it can pick up and respond to stimuli which are ineffective elsewhere.

Similarly, when the presence of an ulcerated duodenum or an inflamed gall-bladder in the upper part of the abdomen makes the whole stomach extremely irritable, we occasionally see hourglass contractions. In these cases it may be that a histological study would show little erosions of the gastric mucous membrane or other sources of local irritation which ordinarily would be insufficient to bring about such contractions.

The presence of the gradient helps to explain the persistence with which the muscle in the lower part of the stomach tends to force the food through the pylorus instead of through the stoma of a gastro-enterostomy. An ideal result might be obtained if, at the time of operation, we could only reverse the pyloric segment of the stomach so that the peristaltic waves would tend to run in the direction of the stoma and not towards the pylorus.

Chapter IX

PRACTICAL APPLICATIONS OF THE GRADIENT IDEA

IF the downward gradient is of value to us in health, it follows as a corollary that upsets in the gradient should produce symptoms of disease. As will be seen later, such upsets have been observed repeatedly in animals, and it is highly suggestive that most of these animals were sickly; some of them were refusing food, and others were even vomiting. The main question before us then is: Are these upsets present ordinarily with the digestive troubles of man, and if so, are they responsible for the disturbances in motility then observed? Unfortunately, these questions cannot yet be answered with certainty. Other factors may easily be more important in some cases. Thus a general increase in the irritability of the bowel might have more to do with the production of a diarrhea than a steepening of the gradient, and other factors about which we know little may be at work. On account of these gaps in our knowledge much of what follows must of necessity be purely theoretical or based on analogy. It seems to me, however, that so long as the reader will keep separate in his mind that which has been proved and that which is merely suggestive, it can do no harm to set forth in a logical manner the various ways in which the gradient may theoretically be upset, and the ways in which such upsets may affect the motility of the tract. After that has been done, it will be easier to analyze the disturbances actually observed with various lesions,

and to see whether or not they agree with those to be expected according to the theory. It is most encouraging to find that they do agree remarkably well in many cases; so well that we now have an easy explanation for many of the observations that have long puzzled the gastro-enterologist, the roentgenologist, and the surgeon.

In many places during the following discussion I may use the word gradient, although the plural, *gradients*, may be a more appropriate term. Perhaps it is a distinction without a difference, because the several gradients are probably all related and interdependent. As I have stated before, my impression is that the metabolic gradient is the underlying one, and it may be that disturbing factors affect it primarily and the other secondarily. I have not as yet sufficient evidence to show that they all change together under the same influences. In a number of the sick animals I have found badly upset gradients of CO_2 production, catalase content, and latent period, with a fairly stable rhythmic gradient. It must be remembered that most of these measurements were made on excised segments, and it may be that the greater amount of trauma and handling incident to the demonstration of the first mentioned gradients served to bring out latent weaknesses in the muscle—weaknesses which did not appear under the more advantageous conditions supplied while counting the rates of contraction. Thus, for the CO_2 estimations, the muscle is stripped from the mucous membrane and is not supplied with sufficient oxygen; for the catalase estimations it is minced, and for the latent period measurements it must be kept in a moist chamber; but in counting the rates of rhythmic contraction one can use either the intact animal with the abdomen opened under salt solution, or excised segments of bowel contracting in warm oxygenated Locke's solution.

FACTORS ALTERING THE GRADIENTS

(1) Irritating Lesions. These include traumatization, inflammation and ulceration (*a*) in the muscle lining the tract; (*b*) in the mucous membrane; (*c*) in the serous coat; (*d*) possibly in the nervous plexus, and (*e*) in the neighboring organs connected with the tract such as the appendix, the gall-bladder, liver, pancreas, and Meckel's diverticulum. We must think also of inflammation and overactivity with vascular engorgement of the organs lying close to the digestive tract, such as the uterus, the urinary bladder, the prostate, the spleen, and perhaps the kidney.

These lesions may affect (*a*) the *metabolism.* It has been shown by Segale,[395] that inflammation raises the metabolic rate of tissues. They become warm because the increase in the rate of oxidation calls for a larger blood supply, and that warms the tissues much as a heating coil would. Cutting or bruising a tissue also raises its metabolic rate. Thus, in planarian worms, Child,[110] found that cutting increased the rate for about twelve hours. (See also Hyman,[209] p. 76.) We know also that a cut or bruised part becomes electro-negative to the neighboring healthy tissue and, as I have noted before, that indicates an increase in the chemical activity (Lillie,[267] p. 181). As Lillie,[266] (p. 441) has pointed out, local injury produces demarcation currents which extend in both directions along the muscle. They exert not only electrotonic blocking influences, but they may directly compensate the action current of an approaching excitation wave and so prevent its effect from extending beyond the point of injury. Garrey has suggested that this mechanism probably accounts for the formation of heart block when only a few fibers in the bundle of His are injured by a pinprick. An increase in the metabolic rate will raise (*b*) the *rate of rhythmic contrac-*

tion. Taylor and I[424] showed that the rate of contraction of an excised segment of bowel varies with the temperature just as a chemical reaction will vary. Once, on opening a rabbit under salt solution, I found a badly inflamed Peyer's patch in the ileum. The affected loop of bowel was cut out and segments of it were put into warm aerated Locke's solution. It was found then that the segment just above the lesion contracted from 21 to 25 times per minute, or more than twice as fast as it would normally have done (Alvarez,[10] p. 347). Inflammation ordinarily increases (*c*) the irritability of a tissue. That it increases (*d*) the *tone* of smooth muscle is easily demonstrated in the digestive tract. The hourglass contraction opposite the site of a gastric ulcer is due partly to the increased tone of the muscle fibers which are stimulated directly by the lesion. The same local action produces the puckered and irritable cap of duodenal ulcer, or the tightly closed sphincter with fissures of the anus.

(2) Ingestion of Food with Distention of the Bowel. All parts of the tract are distended at times by gas; the stomach is distended by food; the small intestine by partly digested material, and the colon by feces, or by enemas. We have seen that distension of smooth muscle generally causes it to contract more actively. A greater activity means (*a*) a *faster metabolism*. That, together with the distension, may increase (*b*) the *rate of rhythmic contraction*. Distension alone will increase the rate in primitive types of hearts (Straub[416]), and I have some evidence that the same thing happens in the bowel. I cannot say as yet just how distension and increased activity affect (*c*) the *irritability*. I do know that after a loop of bowel full of food has been segmenting actively for a while it gets on a "hair trigger" so that a slight stimulus is sufficient to start a peristaltic rush. The

activity incident to digestion has a pronounced effect on (*d*) the *tone*. Mall,[298] p. 45, (see also Cannon,[87] p. 421) pointed out years ago that "if the intestine is at rest it is anemic, small and long; when digesting it is hyperemic, large and short." I have placed two markers 3.5 cm. apart on an active and apparently stretched piece of bowel, and have found them 8 cm. apart later when that region had emptied and quieted down. Cannon ascribes some of this shortening with activity to the "contraction remainder" of smooth muscle; that is, after each contraction the muscle does not relax quite to its previous length.

(3) Nervous Stimuli. Although the digestive tract is largely autonomous, there are undoubtedly many times when the extrinsic nerves affect the progress of material through it. Theoretically these nerves can either depress or stimulate the tract as a whole; they can depress or stimulate one part more than another; or they can depress in one place and stimulate in another. There is some experimental evidence that vagus stimulation will affect the two ends of the stomach differently (May[302]). Some have observed a relaxation of the cardia with an increased activity near the pylorus. This would naturally tend to reverse the gastric waves Spadolini,[406,407] has shown that stimulation of the vagi or of the splanchnics often produces effects which are unequal or dissimilar in different parts of the bowel. Similarly in the heart of the turtle, the sequence of the beat may be upset by vagus stimulation which depresses the sinus while it increases the automaticity of the funnel region (Gault[161]). Wilson[448] produced nodal rhythm in a number of young people by vagus stimulation after the giving of atropin. Apparently the nerve endings in the A-V node were more affected by the drug than those in the S-A

node. Under these circumstances vagus stimulation would tend to reverse the gradient by depressing the sinus more than the ventricle. Lewis[263] (p. 194) states that vagal stimulation alone is sufficient to displace the pacemaker in some people; and Miller[320] (p. 411) and others (Mayer[304]) have found that it will cause vomiting.

There is considerable evidence for the view that a pleasurable psychic stimulus may raise the tone, particularly of the upper end of the tract, and may improve the gradient. We have no data to show that the extrinsic nerves affect (*a*) the metabolism. There is no evidence that they affect (*b*) the rate of rhythmic contraction. They probably tend markedly to depress (*c*) the irritability, so that the muscle will not respond to every stimulus. The most marked changes are seen in (*d*) the tone.

(4) Toxic Depression. Theoretically the tone and activity of the muscle may be depressed by toxins of various kinds, either equally in all parts, or to unequal degrees in different parts. It is possible, also, for a toxin to depress one part while it stimulates another. If the depression is equal in all parts, the gradient will be left intact and the progress of the food may be slowed simply because of the general weakness and sluggishness. This generalized depression may account for the flabby stomachs and intestines which we see particularly in asthenic women. There are many reasons for believing, however, that the depression is often uneven in its distribution, and likely to alter the gradient. Time and again during the preceding chapters I have had occasion to remark on the great difference in the hardiness of the various muscle strips (Alvarez,[2] p. 178 and,[7] p. 426, also,[8] p. 445, also,[10] pp. 346 and 348, also,[11] p. 189, and,[14] p. 65). In the stomach the muscle at the pacemaking region near

the cardia is most sensitive to handling, to electric shocks, to preservation in the ice-box and to all unfavorable conditions; and similarly the muscle in the duodenum is much more sensitive to adverse conditions than is the muscle in the ileum. The muscle of the colon is more hardy, again,

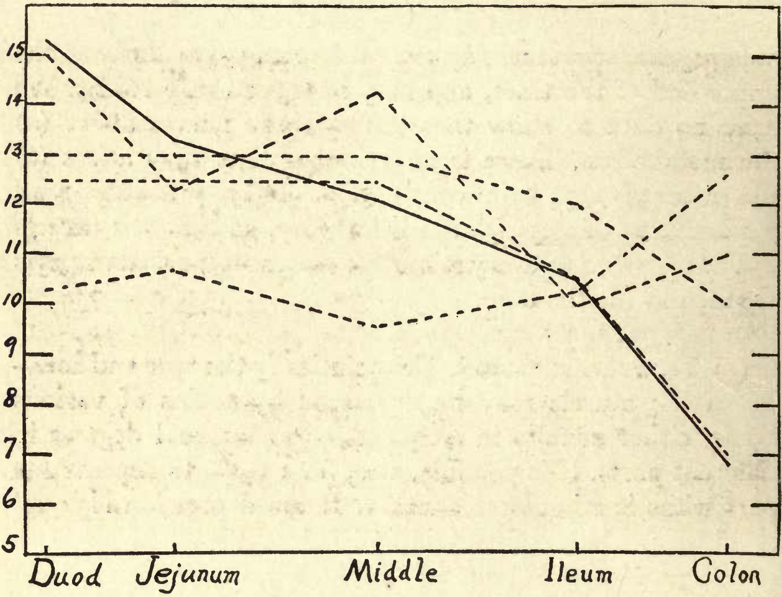

FIG. 15.—Ordinates represent rates per minute; abscissæ represent the segments at varying distances from the pylorus. The solid line represents the average for fifty-three rabbits. The broken lines represent data from sickly animals.

than that of the small bowel. It was found also that the gradients of rhythmicity, metabolism and latent period were reversed in many of the sick animals. Figure 15 shows how the rhythmic gradient may be altered. The segments were removed from rabbits which were heavily infected

either with snuffles, coccidiosis or a cecal whipworm. In these sickly rabbits the segment excised from the duodenal region sometimes would not contract at all in the Locke's solution, although segments from the ileum and colon would do so satisfactorily. Figure 16 shows the difference between the contractions of a healthy rabbit's intestine and those

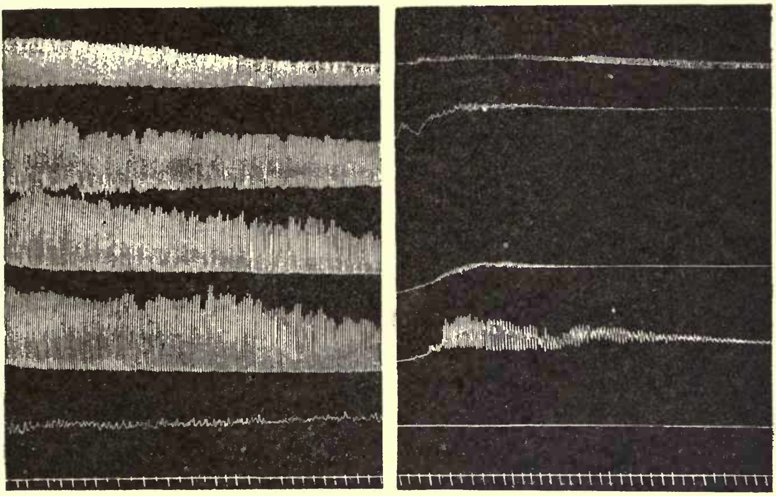

FIG. 16.—Sample tracings from segments from a normal rabbit, on the left, and rabbit purged by castor oil on the right. From above downwards the records are from the duodenum, jejunum, upper ileum, lower ileum and colon. The time record represents thirty seconds.

from a rabbit which had been purged the day before with magnesium sulphate. In this case the amplitude is much affected. Figure 8 shows on the left side the usual gradient of latent period found in normal dogs, and on the right the gradient found in distempered dogs. It is apparent that the muscle in the duodenal segment suffers most, and that the muscle from the ileum is even stimulated by the toxins,

whatever they are. A similar difference was observed in the stomachs of sick animals; that is, the segment from the cardiac end would be insensitive and sluggish while the segment from the pyloric antrum would contract even more promptly than it normally does. Naturally, this drop in the upper end with a corresponding rise at the lower would tend very strongly to reverse the gradient.

It may be that the effect of the toxins is primarily a stimulating one, and that the ileum and antrum profit by it because their original tone is low. At the upper end, however, the tone of the muscle is probably so nearly maximal that further stimulation pushes it over the limit of safety, and the tissue is damaged. I have some pharmacologic evidence in favor of such a view, and there are many analogies in the biological literature.

Anyone who attempts to do any work with the intestinal muscle will I think soon be impressed with these marked changes in the sickly animals and will realize how necessary it is in such experiments to secure really healthy ones. The same precaution must be taken when studying the heart. It is well known that preparations from thin or sickly animals or from animals kept too long in the laboratory will not beat satisfactorily. Frogs and turtles should not be used during the summer or during the mating season (Stiles,[412] p. 341; Schultz,[391] p. 126). Hunter[195] found that he could not use Salpae kept in the laboratory for any length of time because their hearts beat at both ends simultaneously. Dr. Cohn of the Rockefeller Hospital tells me that a large proportion of the dogs studied in his laboratory show nodal rhythm. Eyster and Meek,[146] Halsey[178] (p. 731) and Cullis and Tribe[122] remark on the same thing. Similar displacements of the pacemaker have been observed in man in various asthenic states (Williams and James,[447] Hart[179]). The evanescent

nature of these upsets in the cardiac gradient, and the fact that sometimes at autopsy no local lesions are found, makes me think that the displacement of the pacemaker may be due to an unequal effect of fatigue or disease toxins on different parts of the heart. It is well known to athletes that a little fatigue or infection, a sleepless night, a slight cold or diarrhea, will greatly diminish the efficiency of the heart and skeletal muscles.

After I had for some time been studying the upsets of the intestinal gradient due to the unequal effects of disease toxins, I discovered that Dr. C. M. Child had been making similar observations on the lower forms of life. I have already reviewed a good deal of his work in the chapter on gradients. Dr. Child[112] argues that tissues with a high metabolic rate and a large need for oxygen must suffer more from a scarcity of that oxygen than do tissues with a low rate. The supply of the gas can be curtailed either by interfering with the circulation and pulmonary respiration or by giving a poison like KCN which keeps the oxygen from combining with the protoplasm of the cell (Hyman,[208] p. 340). Child has found that weak solutions of KCN may be used very conveniently to demonstrate the presence of gradients of metabolism, because the tissues with a high rate become paralyzed and die first; and the others with slower rates follow in order. Thus if planarian worms of different ages are put into .0065 per cent KCN, the younger ones with the higher rates of oxidation die before the older ones. If hydras are submitted to the same test the more active ones die first. Similarly, young animals and babies with their fast rates are more susceptible to anesthetics than are old animals and old men (Symes[419]). Glaister and Logan[167] note also that in coal mines the boys are more likely to succumb to CO poisoning than are the older men.

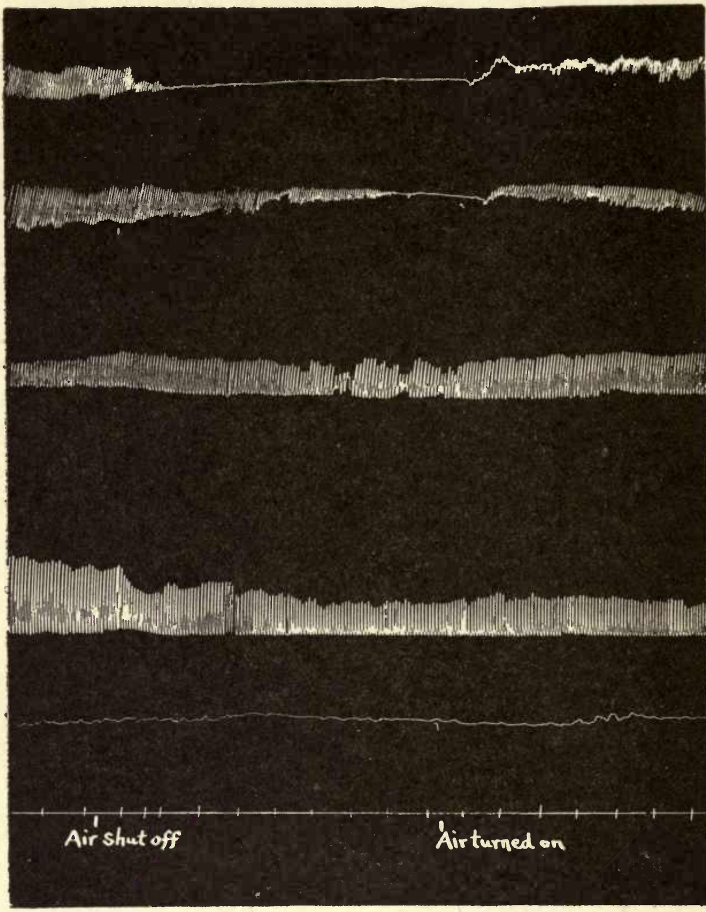

FIG. 17.—The effect of asphyxia on segments from different regions. From above downward the segments are from the duodenum, jejunum, middle ileum and colon.

Following this line of reasoning, Child put into dilute solutions of KCN a small water organism which swims with the help of comb-like rows of large cilia which are arranged along its sides. The damaging effect of the KCN was so much more marked at the pacemaking end that the impulse was sometimes left to begin at the other pole of the animal; the sequence of the beat was reversed, and the animal swam backwards.

After reading about this work of Child I put five segments from different parts of the bowel into warm Locke's solution, and after they were all contracting well I shut off the air which had been bubbling through the solution (Alvarez and Starkweather[11]). Figure 17 shows how markedly this affected the activity of the duodenum and jejunum and how little it affected that of the ileum. As was to be expected, a trace of KCN added to the solution produced much the same type of graded depression (Fig. 18).

It appears that the heart muscle also shows a graded response to asphyxia. We would expect the sensitive pacemaking region to suffer most, and actually Lewis and Mathison,[265] have found that the auricle is slowed, the ventricle is accelerated and dissociation is produced. These changes are brought about locally, and are unaffected by curare, atropin and vagal section. On the return of respiration, recovery is generally prompt and complete. Similarly, in hibernating dormice Miss Buchanan[76] found that the ventricles beat alone, but as the animal wakes and begins to breathe more rapidly, the P waves (auricular) appear in the electrocardiogram. After a while the gradient is restored and the auricle takes the pace. When the animal breathes in Cheyne-Stokes fashion, the P waves disappear during the periods of apnea. Greene and Gilbert[169] found also while studying the hearts of aviators subjected to the rebreathing

test, that when the oxygen supply was greatly lowered the S-A region was the first to fail.

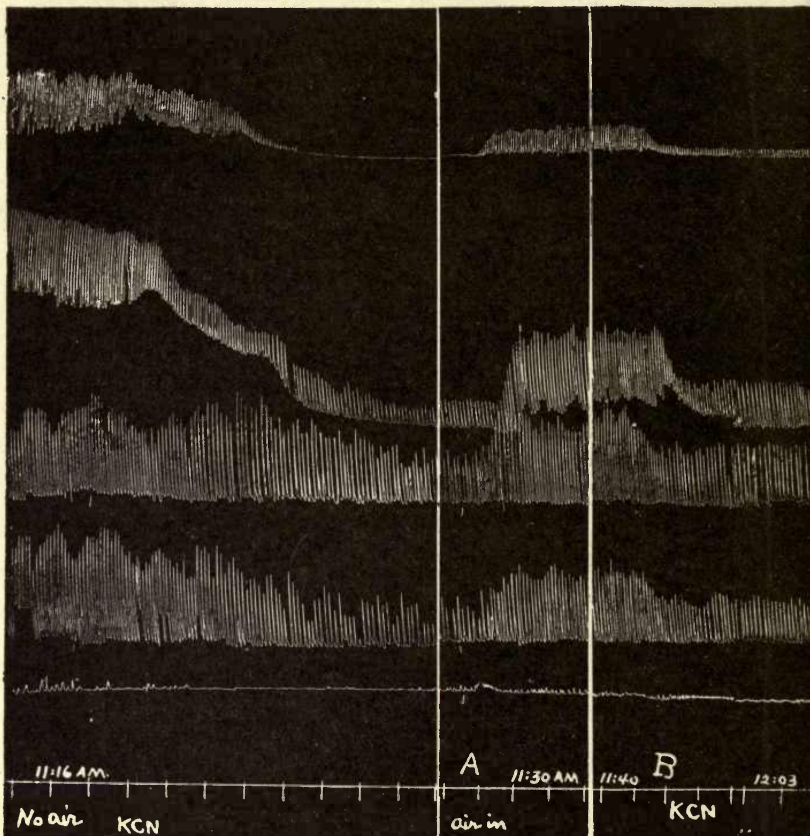

Fig. 18.—Effect of KCN on segments in non-oxygenated Locke's solution. At *A* air was allowed to bubble through the solution; At *B*, more KCN was added.

Raasche[370] has shown with the excised heart that chloroform can paralyze the auricle in dosages which only decrease

the amplitude of the ventricular contractions, and it may be that some of the stoppages of that organ after anesthesia are due partly to a reversal of the rhythmic gradient (Fig. 19). Some of the other cardiac poisons, and perhaps some of the disease toxins show signs of acting in this disturbing way.

Tashiro[422] has recently brought forward considerable evidence to show that anesthesia, particularly in nerve

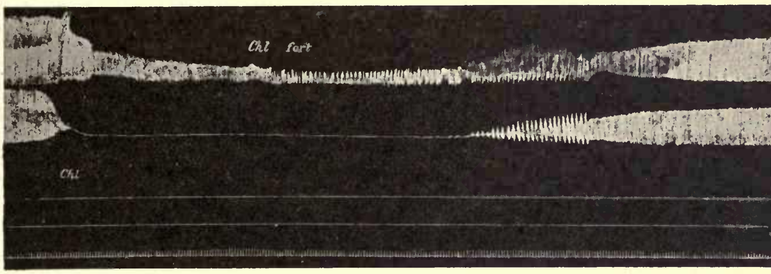

FIG. 19.—The upper tracing is from the left ventricle; the lower is from the left auricle. Time marking represents records. Note greater effect of chloroform on the auricle. (*From Raasche.*)

trunks, may be due to a similarly produced reversal in the metabolic gradient along the nerves. Much work must yet be done before such a theory will be generally accepted, but in view of the many analogies, the idea is a very attractive one. He explains perfectly some of the puzzling phenomena of conduction through anesthetized stretches (Niwa[342]). There are so many practical applications of this idea of gradient reversal under the action of drugs and toxins, that I believe it must be used more and more as men come to know about it. It offers the simplest and easiest explanation for many phenomena which have hitherto been explained in roundabout ways, as by bringing in a complicated system of nerves, the workings of which are not really understood.

I think there is no doubt that digestive upsets in the sick are due in part to influences coming through the extrinsic nerves, but when one can demonstrate a marked reversal of the gradient in small excised segments of gut, and when one can tell by studying such segments whether they have been removed from a sick or from a healthy animal, I think the most devoted follower of Eppinger and Hess[142] must admit that the local changes have some significance. I believe that the upsets in the gradient which are so easily demonstrated can explain the loss of appetite, the disgust for food, the nausea and the vomiting seen in infectious diseases and asthenic states. The distempered dogs and snuffling cats often refuse food. If some is forced on them it may stay in the stomach for hours or days. This has been commented upon by Cannon and others. In autopsies on people who have died with botulism, food has been found in the stomach which was eaten many days before, when the trouble commenced. Similar stagnation is often noticed in the stomachs of men and women with tuberculosis and other infectious diseases. As in many of these cases I find the pylorus patent and can see good peristaltic waves, I cannot get away from the idea of a flattened gradient. Later when such patients go on vacations, take rest cures or get over their infections, their appetities return, they are able to digest the roughest food; and I believe their gradients have become normally steep again.

It is well known to all clinicians that most men with failing hearts have indigestion and flatulence. Remembering the upsetting effect of asphyxia on the gradient, it has occurred to me that a chronic passive congestion, interfering with the oxygen supply to the intestinal muscle, might easily account for much of the trouble. It is possible, of course, that some of the disturbance is due to stimuli coming

down the vagus, but we know much less about the way in which such stimuli act than we know about the way in which asphyxia acts. Nausea is often a marked symptom in acute decompensations of the heart, and in a subsequent chapter the reasons will be given for believing that that means mild reverse peristalsis. Nausea and vomiting are prominent symptoms also in subacute CO poisoning, in which case the intestine must share in the general asphyxiation of the tissues.

(5) Drugs. Very little is known as yet about the effects of drugs on the gradient. This is due, of course, to the fact that it has not yet occurred to pharmacologists that a drug might upset the dynamic equilibrium of the intestine by stimulating or depressing one part more than another. To be sure, we speak of certain purgatives as acting principally on the small bowel or on the large, but after reading very extensively on the subject, I can find no statement which suggests that any one has thought of purgation as being due to a lowering of the tone of the lower end of the colon.

Figure 20 shows that the action of adrenalin on the intestinal muscle is a purely depressant one, and that it is graded from duodenum to ileum. I was able to show that it is a depressant also when given intravenously to man, and yet we know that it often acts as a purgative. In a woman with a large ventral hernia, which left the ileum easily visible under a thin covering of skin, adrenalin produced a transient cessation of rhythmic movements which was followed by the appearance of some peristaltic rushes, and later by a summons to empty the bowel. It seemed to me that the rush waves might have been brought about by an unbalanced condition of the gut due to the persistence of activity in the duodenum at a time when the ileum and colon were paralyzed. Magnesium sulfate is another muscular depressant

which shows a graded effect on the segments, and which purges. Here, however, the pronounced effects on the

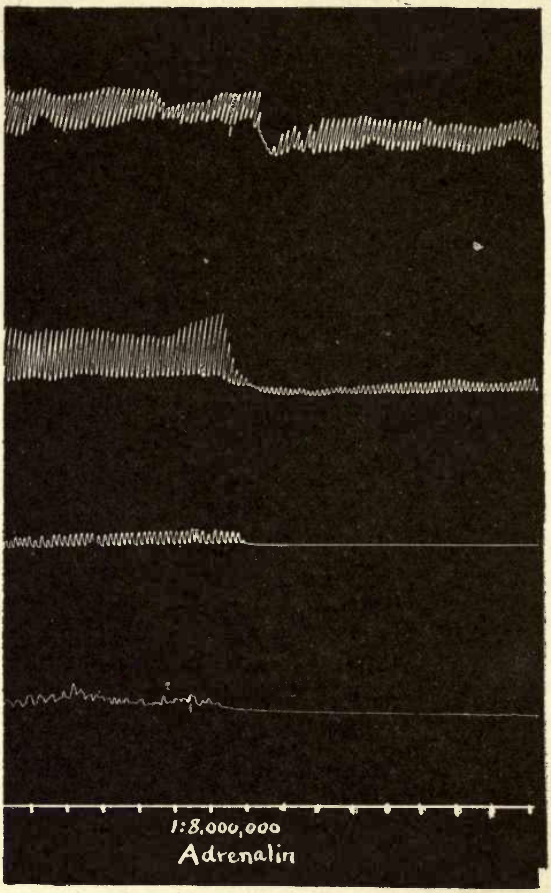

FIG. 20.—The graded effect of adrenalin. From above downwards, the segments are from duodenum, upper ileum, lower ileum and colon.

absorption of fluid from the mucous membrane are probably much more important factors in producing the diarrhea.

I have studied the effects of some seventy-five different drugs on excised segments from different parts of the bowel, (Alvarez,[12] and also[16]) and have found definite regional differences with many of them. Much work must yet be done, particularly on the intact animal, before we can say whether these differences have any practical significance. It is only suggestive that a number of the drugs whose action on the segments, if duplicated in the intact animal, would tend to reverse the gradient, are emetics; and many of those that would tend to steepen it are well known laxatives. Pharmacologists would probably remind me that almost all of the emetics have been shown to act directly on the vomiting center in the medulla. Eggleston and Hatcher[135] have shown conclusively that even an eviscerated dog which has no digestive tract between his diaphragm and his anus will retch when given apomorphin. It is worth noting, however, that some of the drugs, which in large doses produce emesis, in small doses produce regurgitation, heart burn, belching and nausea, which as I shall show later, are probably signs of mild reverse peristalsis. It seems to me that these drugs may perhaps first reverse or flatten the gradient in the bowel; and that the disturbances thus produced may finally so influence the center in the brain that it calls into action the voluntary muscles and brings about the coordinated vomiting movements.

It is interesting that the ancients used purgatives to restore the downward gradient after they had produced too violent and too lasting an emesis, and similarly they gave emetics to try to stop violent purgation. When the ancient Egyptians wanted to see if a woman was pregnant they gave her pounded watermelon in milk. If she vomited, the test was supposed to be positive (Neuberger[340]). Possibly a mild emetic insufficient to turn a healthy person's stomach

might be sufficient to reverse peristalsis in a woman whose gradient was already somewhat upset by the pregnancy. As I shall point out later, there is some evidence that the gradient is actually flattened or reversed in some pregnant women.

I think it is quite possible that certain laxatives, especially calomel, help the "bilious" not because of any action on the liver, because that has been pretty thoroughly disproved; but by restoring the downward gradient which has been upset, perhaps by the overactivity of a distended colon. It may be that drugs like eserin and pilocarpin which produce active peristalsis do not serve well as purgatives because they stimulate all parts of the tract equally. Katsch[226] (p. 287) who watched the contractions of the bowel through glass windows in the abdominal wall, was impressed with the fact that although these drugs greatly increased the activity of the muscle, they did not cause much movement of material from one loop to another.

Ways in which the Various Factors can Alter the Gradient. Theoretically the gradient as a whole may be made more steep, less steep, level or reversed. Each of these changes may be brought about in three different ways. Thus, the gradient may be steepened by raising the upper end, by depressing the lower end, or by doing both at the same time. The gradient may also be altered in sections. Thus in cases of vomiting with diarrhea it may be that some point in the middle of the bowel has become very irritable so that the gradient slopes away from it in both directions. A lesion producing a slighter degree of local irritability may make only a small "hump." The gradient might also be interrupted by what may perhaps be termed "deep holes." Thus in a number of purged rabbits, short sections of bowel

were found which would not react at all to strong electric currents or pinches, while the adjacent bowel on either side was very irritable. Theoretically food and gas might become trapped for a while in such weakened segments (Alvarez and Taylor[23]).

Stimulation at the Upper End with Possible Steepening of the Gradient. It may sound like a Hibernianism, but it does seem that food goes down the tract more easily because it is put in at the upper end. A rise of tone in the stomach and duodenum tends to make the gradient of forces steeper down the bowel. There is some evidence that a barium meal will go down the bowel faster if it is followed by a second meal given shortly afterwards (Hurst,[202] Ludin[281]). The second meal probably tends to maintain the high tone at the upper end. There is also considerable evidence that pleasurable psychic stimuli still further raise this tone. Several observers have stated that contrast meals leave the stomach more rapidly if they are made palatable (Hurst,[202] Gilmer[165]). Haudek and Stigler[180] (p. 159) thought that the emptying of the stomach was slower when the food was taken with disgust. Takahashi[421] showed that a cat's stomach emptied half as fast when the animal was fed with a spoon as when it ate by itself. Sailer (Worden et al.[452]) thought that the bismuth meal left the stomach more quickly when the patient drank it than when it was given by stomach tube. I observed in a patient with a jejunal fistula that the contractions of the bowel were more active when the patient ate by himself than when a nurse fed him. The latter method of eating was plainly annoying to him. One of my patients with an incompetent anal sphincter generally had one or more bowel movements immediately after either eating, smelling, seeing or even thinking pleasurably of food. It

has been shown that sham drinking, particularly in thirsty animals, will cause water to leave the stomach of a dog much faster than it otherwise would (Best and Cohnheim,[52] p. 116). The dog drinks in the usual way, but the water runs out through an esophageal fistula in the neck. The water in the stomach is put in through a gastrostomy opening. Such sham feeding will also prevent the backflow into the stomach which occurs when fat is introduced into the duodenum through a fistula (Best and Cohnheim,[51] p. 125). This is explainable if the plesaure of drinking has caused the tone of the stomach to rise above that of the duodenum.

Jonas,[218] several years ago remarked on the rapid progress of food through the small intestine, and the diarrhea which may appear when the stomach empties too rapidly. Hence he speaks of the stomach as the "Hauptmotor" for the intestine. (See also Surmont and Dubus.[417]) A similar hypermotility with even fatal diarrhea has been observed occasionally after gastro-enterostomies when the stomach emptied too rapidly (Hurst,[204] p. 466; Moynihan,[330] p. 221). This steepening of the gradient by rapid overdistension of the duodenum may be largely responsible for the diarrhea of people with achlorhydria. The reason that it occurs generally in the morning may be that the bowel is then most irritable and responsive on account of the night's rest. There may, of course, be other factors—the intestinal contents may be more stimulating on account of defective chemical digestion, abnormal temperature, abnormal osmotic pressure, or abnormal bacterial content.

If, on the other hand, the gastric peristalsis is weakened and the emptying of the stomach slowed, the progress of material through the bowel is often slowed. Dagaew[126] found in dogs that when the strong antral muscle is removed, the food reaches the lower ileum in thirteen hours instead

of six. Similarly, in a human case, Cohn[115] found that after complete removal of the stomach and vagus endings the food took twenty-four hours to reach the cecum. Cole[119] (p. 110) has remarked also on the slow emptying of the cecum if the patient fasts after taking a barium meal.

There is some evidence that actual reversal of the gradient may take place during starvation if the tone of the upper end of the tract falls markedly. This may account for the nausea experienced by many people when they are hungry. Boldireff[62] states that in animals which have fasted for some time, intestinal juice will run out of a gastric fistula continuously in large amounts.

There is no doubt that irritant lesions increase the tone and activity of the upper end of the tract. In the presence of a duodenal ulcer, not only the duodenum, but the whole stomach often becomes irritated so that it shows four or five waves at a time. A similar hypermotility is observed in some cases of gall-bladder disease. In these cases the head of the barium column is often found at the splenic flexure after six hours, which is exactly what we would expect if the gradient has been steepened.

Theoretically a duodenal or pyloric ulcer should slow the progress of material coming towards it from the stomach, and, when irritant enough, it should reverse the gastric waves. Actually we do find in many of these cases a six-hour residue in the stomach and, more rarely, we see the reverse waves. Occasionally I have seen wave-like contraction rings arising in the stomach, perhaps moving downwards a few centimeters and then fading out as if they were blocked from advancing farther. Unfortunately the picture is complicated by a number of factors. One of these is probably the connective tissue barrier at the pylorus. As that line of division, together with the difference in the muscle on the

two sides, stops the progress of waves downward, it probably tends to block some of the influences passing upwards. Many of the six-hour residues are due almost entirely to a mechanical blocking of the pylorus by the lesion. In other cases we find that the stomach empties unusually rapidly during the first few minutes, and after that, there is marked stagnation for hours. In these cases, it seems to me that the hypertonic stomach, distended and stimulated by the food, is able to overcome the back pressure from the ulcer. After that stimulus is partly gone, the irritation of the ulcer, with the change in the gradient, is able to hold back a residue in the stomach, perhaps until that organ is sufficiently distended again by food.

When a stomach is greatly distended, owing to the presence of a stenosing ulcer at the pylorus, the point of origin of the waves may be affected also by differences in the pressure sustained by different parts of the muscular wall. Other factors will be found discussed in Chapter VIII. Carcinoma ordinarily seems to grow without irritating the surrounding muscle very much; in fact, it may even depress it. Hence it is, perhaps, that the gradient often remains normal, and symptoms are not produced until the tumor acts mechanically.

THE MECHANICAL CONTROL OF THE PYLORUS. The idea of a gradient is helpful also in studying the peculiarities of pyloric action, particularly in disease. Cannon[83] showed many years ago that one of the factors controlling the sphincter is a chemical one; that is, an increase in the acidity of the stomach tends to open the pylorus, and an increase in the acidity of the duodenum tends to close it. This mechanism seems so simple and so appropriate that some writers make the mistake of considering it to be the only factor at

work. This is in spite of Cannon's[82] (p. 570) statement that "in whatever manner the pylorus may act under normal conditions, that action can certainly be overcome in abnormal states." Cannon realized that his experiments did not throw light on some of the peculiarities of gastric emptying in achylia and in the presence of ulcers and carcinomas. Recently a great deal of the theorizing based upon the idea of an alkaline duodenum has been upset by the work of McClendon,[309] Long and Fenger,[273] and others who have shown with the help of modern electro-chemical methods, that the contents of the upper intestine are normally slightly acid. In animals with short intestines they may be acid even as far as the ileocecal sphincter. Furthermore, a number of those who in recent years have studied the emptying of the stomach in man have come to the conclusion that especially in disease, the hydrochloric acid has little to do with the pyloric control (Von Bergmann,[49] Faulhaber and von Redwitz,[149] Egan,[134] Morse,[328] Wheelon and Thomas,[444] Luckhardt, Philips and Carlson,[277] McClure, Reynolds and Schwartz,[311] Spencer, Meyer, Rehfuss and Hawk,[408] Lenk and Eisler[260]).

It seems probable, from a great deal of experimental work, that the opening and closing of the pylorus depends to a large measure on mechanical factors, that is, differences in the gradient of tone and irritability between the stomach and duodenum. I have already mentioned the experiments which show that an increased pressure brought about by pleasant psychic influences will cause more rapid emptying. An increase in the amount of distension of the stomach may have a similar effect. Thus Marbaix[300] found that 250 c.c. of water left his stomach twice as fast if he put 250 c.c. of air on top of it. Ludin,[281] Moritz,[327] and others have found that food eaten on top of a contrast meal causes that to leave

the stomach more rapidly. Cohnheim and Dreyfus[118] (p. 58) found in the dog that when little food was present in the stomach 10 c.c. of gastric contents injected into the duodenum through a fistula closed the pylorus for from ten to fifteen minutes; but when the stomach was full of fluid, the same stimulus stopped the flow for from one to one and one-half minutes. The distension of the duodenum by a balloon (Tobler[426]) or by food, or the irritation of the bowel by strong saline solutions, retarded the emptying of the stomach. Cohnheim and Dreyfus[118] (p. 58) put 4 per cent solutions of sodium chloride and magnesium sulphate through a fistula into the upper bowel and produced marked slowing of gastric emptying, nausea and even vomiting. Baumstark[37] produced a similar slowing when he put fermented food through fistulae into different parts of the small intestine. Similarly no food left the stomach of an animal for five hours after Cannon and Murphy[93] (p. 515) made an entero-enterostomy 18 cm. below the pylorus. All these procedures probably raised the tone of the intestine above that of the stomach. When the bowel quieted down or partially emptied itself of food the stomach was able to empty again. It is this type of activity which keeps the food from pouring out of the stomach after gastro-enterostomies and pyloroplasties (Cannon and Blake,[92] p. 708; Marbaix,[300] p. 283; von Gehuchten,[163] p. 277). If this retarding effect from the bowel is eliminated by allowing the food to escape through a duodenal fistula, the stomach empties very rapidly (Hirsch,[189] p. 382).

Towards the close of a meal or during starvation it appears that the tone of the stomach drops below that of the digesting bowel, because we know that the duodenal contents then flow back into the stomach (Kussmaul,[247] Rehfuss, Bergheim and Hawk[372]). This back-flow can be accentuated by eating

fats (Boldireff,[62] p. 457), perhaps because while they impair the tone and motility of the stomach (von Tabora,[420] Cannon,[83] p. 315) their fatty acids, split off by the pancreatic juice, stimulate the bowel (Bokai[61]). Neilson and Lipsitz[339] have shown also that bodily activity and posture have some effect on the emptying time of the stomach.

Stimulation in the Middle. We have seen that a stimulus which raises the tone in the middle of a loop sends off waves in both directions. Hence it is not surprising that food put into the middle of the tract tends to go both ways. Thus in jejunal feeding, unless the food is put in very slowly and exactly at the body temperature, there will often be nausea, regurgitation of the material, and even vomiting (Kelling,[234] p. 248; Wegele, Gross and Held,[442] p. 272; Stockton,[413] p. 81). In some cases observed by me the patient's discomfort was relieved only by giving a little food by mouth just before the feedings. This perhaps raised the tone of the stomach to its normal position above that of the jejunum. In a case of jejunal feeding, nausea, vomiting and colic were produced by giving a Murphy drip of glucose and salt solution. When this was stopped, the patient had no further distress until one day when he had a cleansing enema. In that case the lower end of the gradient was probably raised too high. It is common knowledge that vomiting is often associated with diarrhea. Thus, a small boy who had eaten his fill of black-berries vomited three-fourths of the amount twelve hours later, and shortly after that the remainder was voided in loose bowel movement. Probably enough of the irritant material got into the jejunum at the start to raise the irritability there and to prevent the stomach from emptying. Finally the tone became high enough in the upper bowel so that it could clear itself in both directions. The vomiting and diarrhea with seasickness, or after strong

psychic stimulation might be due, at least in part, to a rise in tone of the jejunum at the point where it is so richly supplied with vagus fibers (Bayliss and Starling,[39] p. 141; Colin Mackenzie,[286] and also[287] p. 287, Jacobj,[213] p. 198).

Lesions in the course of the bowel may make the affected area so irritable that the barium meal will stay out of it (Stierlin[411]). Thus Kienbock,[235] and Case[106] (p. 381) have remarked on the emptiness of the cecum in cecal tuberculosis. Nothnagel[343] (p. 39) found that food was rushed through sections of bowel which he irritated by the injection of concentrated salt solution, and White[445] made similar observations with croton oil.

If the gradient is reversed above an irritated place in the bowel, as the theory demands, we should expect the "reversed" segment to remain empty, and actually we do find that food does not pack up against an *intestinal obstruction* unless it is due to a carcinoma or some other slowly arising and non-irritating cause, i.e., something which does not affect the gradient (Kirstein,[237] Kelling,[234] Maleyx,[297] Reichel,[373] Nothnagel,[343] p. 29; Quirot,[368] p. 25; Shimodaira[399]). The more irritating the lesion, the wider the empty zone, and the farther orad do we find the signs of back-pressure. Years ago Kirstein[237] came to the conclusion that the symptoms of acute ileus are not the result of closure of the bowel but of its maltreatment. When he cut the ileum across and sewed it up, food went on down and packed against the obstruction; the dogs did not vomit and did not seem sick. When, however he pinched the bowel with an elastic ligature the food was held back far above the lesion and the dogs were very sick. Treves[434] (p. 2) noted also that in acute intussusception violent symptoms of obstruction often appear, although at operation little narrowing is found in the lumen of the bowel.

In other cases of intestinal obstruction no organic narrowing can be found, and the cause is said to be "dynamic." The following experiment shows that intestinal obstruction can occur without any narrowing of the lumen at all. I took a rabbit's intestine, exposed under salt solution, and pinched the lower ileum with a hemostat, so as to bruise a narrow ring. The diameter of the lumen was in no way altered. The abdomen was closed. The animal was kept under urethan anesthesia, and was opened again several hours later. It was then found that no food had passed the injured place, although the bowel above was markedly distended and was contracting violently. Waves approached within 10 or 15 cm. of the site of the lesion, where they either faded away or broke against reverse waves. The bowel immediately above the lesion contained only a little gas. I concluded that the gradient was uphill for some distance above the bruised tissue. Kelling[234] was actually able to show such a reversal by tying manometers into the bowel at different levels above an experimentally produced obstruction.

The fact that the segment of bowel immediately above the site of obstruction contains nothing but gas has been commented upon by some surgeons who have come to the conclusion that in bad cases, enterostomies should be made high above the lesion if any drainage of fluid is to be expected. Other surgeons have noticed that gastric stasis and dilation appear early in the course of intestinal obstruction. They have washed large amounts of intestinal contents out of the stomach some time before the reversal of the gradient was marked enough to produce fecal vomiting (Ewald,[144]). We see then that the gradient idea throws great light on the peculiarities of intestinal action in ileus, and in its turn, receives much support and confirmation.

Stimulation at the Lower End. The commonest lesion found at the lower end of the small intestine is appendicitis. This disease can produce all grades of back pressure from a slight ileac stasis, demonstrable by the roentgen ray, to the vomiting of large amounts of intestinal fluid. Just as the emptying of the stomach tends to produce an emptying of the lower ileum into the cecum (Hurst,[199] p. 34, also,[203] p. 55), so it appears that an early emptying of the ileum may favor the emptying of the stomach, and a late emptying of the ileum may slow the emptying of the stomach (Cole,[119] p. 109, Barclay,[35] p. 643). Considerable experimental work has been done on the subject by Hedblom and Cannon,[182] and later by White.[445] They found in cats that they could slow the progress of food through the stomach and small intestine if they irritated the cecum sufficiently with croton oil. Mild degrees of irritation produce no effect on the emptying of the stomach. Similarly in man, much depends upon the degree of irritation produced by the lesion; upon the stage in which we find the disease, and upon the original stability of the gradient in a particular individual (Borgbjarg,[64] Barclay,[34] p. 234; Paterson,[352] p. 197; Smithies,[404] p. 187). Thus in an interval between attacks we may be unable to detect any abnormality in the fluoroscopic picture; in a subacute case there may be loss of appetite, nausea and some gastric and duodenal stasis, and in an acute case there may be persistent vomiting. I remember, however, a strong, stout young woman, with a good appetite, who walked around for several days with an "exploded" appendix. Even during the height of her pain she had no nausea, she did not vomit, her appetite remained good and she noticed only a coated tongue, bad taste, a tendency to fill up quickly after eating, and some diarrhea. Apparently the gradient of this robust girl was so good that even a pericecal

abscess could not reverse it. All it could do was to steepen the gradient below the lesion. Theoretically, we should always find a more rapid emptying of the colon with appendicitis, and we do see it quite often in children. According to Deaver[124] (p. 226 and 244), it is present in adults in only 13 per cent of the cases. Apparently other factors come in to neutralize the tendency.

Some of the most violent forms of reverse peristalsis in the tract are due to the irritation of the sigmoid flexure caused by volvulus. I once saw a woman who (after eating shell fish) vomited so violently and so continuously for about a week that she died. At autopsy the only thing that could be found was a small patch of markedly inflamed mucous membrance in the sigmoid flexure. Vomiting can be produced by irritating or distending the colon with enemas. Several writers (Rolleston and Jex Blake,[376] Bine and Schmoll[60]) have commented on the vomiting which not infrequently occurs with rectal feeding. The more irritating the enema is, the more likely it is to cause trouble. Several of my patients get nausea with ordinary injections of water or normal salt solution, but they vomit when soap, glycerine, turpentine or glucose is added to the solution. I have long felt that the Murphy drip is responsible for some of the distress and nausea suffered by people after abdominal operations, and my experience makes me feel that it should be used only when necessary to replace water lost by bleeding and vomiting. Especially after operations in the pelvis, nothing should be put into the rectum which will tend to raise its tone still farther and to upset the gradient.

Constipation. There are good reasons for believing that normally the tone of the rectum and sigmoid is higher than that of the cecum or of the ascending colon (Alvarez

and Starkweather,[17] Rost,[378] p. 992). This tends to protect the anal sphincter and to keep feces from packing into the ampulla excepting during those times—as after breakfast—when the pressure from the upper part of the tract is very great. If defecation is postponed, it can occasionally be shown with the roentgen ray that the feces have returned into the sigmoid or even into the descending colon (Schwartz,[394] Drummond,[130] Kästle and Bruegel[223]; personal observations). The commonest cause of constipation is probably an increase in the tone of the rectum which makes the gradient steeper up to the anal ring (Singer and Holzknecht[401]). Anything which keeps up an irritation in the lower colon, such as hemorrhoids, fissures, fistulae, or a diseased ovary, uterus or prostate, can easily bring about or exaggerate constipation. Ordinarily constipation seems to be a nervous disease; the stagnation is almost always in the rectum, and the increase in tone of the sphincters seems to be a part of that general increase in tension of the voluntary muscles which is observed so commonly in constipated people.

The writers on constipation generally classify the cases into atonic and spastic. In the first type, the colon is supposed to be too weak to force onward its contents; in the second, it is supposed to be so irritable and strong that it will not let these contents go by. So far as I can remember I have never seen an atonic case; they all seem to be spastic. The believers in the atonic type of constipation will moreover find it hard to reconcile their views with the observations of Müller and Hesky,[334] who removed all the muscle from the colons of dogs and found that it produced very little disturbance in motility. Apparently the muscle of the small intestine was strong enough to force the material onward through the inactive segment, and the only thing to hold it back was the muscle around the anal canal.

Depression at the Lower End. So far we know very little about alterations in the gradient due to depression at the lower end. I have seen some cases of diarrhea which seemed to me to be due almost undoubtedly to the loss of tone of the lower end of the bowel following extensive operations for fistula in ano. In these cases, every stimulus from above produced a bowel movement. Normally, such stimuli probably produce a surge towards the rectum which is taken up or thrown back by the tonic state of the lower bowel. If this influence is removed by making a large fistula into the lower ileum, the food will go through the small intestine too fast (Demarquay,[125] Macewen[285]). It is suggestive that in most cases of diarrhea the colon is atonic. This can be seen not only with the roentgen ray but it shows itself also in the ease with which a sigmoidoscope can be thrust far into the bowel. On the other hand, in the constipated, the anal sphincters and sometimes the whole rectal wall are exceedingly tonic; the roentgen ray shows a narrow lumen with marked haustration, and the sigmoidoscope is gripped firmly. A serious objection can be found to this line of argument in the work of Müller and Hesky,[334] quoted in the preceding section. Theoretically, the removal of the colonic muscle might easily cause diarrhea, but according to these investigators, such diarrhea is transient and generally gives way to slight constipation. The problem must be studied further.

An Illustrative Simile. Some who find it hard to understand what a gradient of forces is and who have difficulty in following the argument as I have outlined it in the preceding pages may be helped by the following somewhat grotesque simile:

Let us imagine a game of push-ball played by a column of

men who have been graded according to their metabolic rates. At one end they are young, wide awake and active; at the other end they are old and comparatively sluggish in their movements. These men will represent the muscle fibers along the bowel. The first young man takes the ball and tries to push it past the second. The second resists, but is soon overcome owing to the greater activity and aggressiveness of Number 1. As soon as the ball passes Number 2 he joins with Number 1 in trying to push it past Numbers 3 and 4. Once past them, Number 1 and Number 2 rest while Number 3 and Number 4 push it past Number 5 and Number 6; and so it goes. The men in the first third of the line (jejunum) play incessantly so long as the ball is near them, and they soon force it down among the old men. These play only at intervals, often letting the ball lie quiet while they rest. New balls are sent down the line from time to time so that the old men generally have three or four on their hands at once. They are aroused to get rid of one or two of these when they see that a new one has started down (ileocolic reflex and defecation).

Usually the ball moves in one direction and there is little likelihood that the old men with their intermittent efforts will ever overcome the youths, but one day some of the old men are so stimulated by some drug that they play fast and furiously, and the others cannot push the ball anywhere near the lower goal. On another occasion some of the old men are injured and this stimulates their comrades to greater efforts so that the injured ones will be relieved for a while from the trouble of handling the ball. Their efforts may be so strenuous that the balls are thrown out the way they entered. On still another occasion, a cloud of poison gas is liberated over the players. All are weakened and some become ill, but the young men who breathe faster are more

susceptible to the poison and suffer more from the lack of proper air than do the old men. Until they recover, the game is slower, but the old men are now relatively more active than the young ones and the ball is sometimes sent back to its original starting place.

A change in the play is brought about also when the balls are made unpleasant or painful to handle. Perhaps they have been filled with pepper or studded with sharp spikes. The first one or two to start down the line are rushed through, so that the players can get rid of them as rapidly as possible. The men are then so irritated by this annoyance that they throw back the next few balls that are offered them (diarrhea and vomiting).

Some physicians at first confuse the gradient of forces with the gradient of gravity due to the position of loops of bowel in the abdomen. Returning to the simile, it will be seen that if the game of push-ball is being played on the side of a hill it will make little difference whether the young men are above or below the old. The position of the line is not the important thing because the essential factor determining the movements of the ball is the gradient of activity and strength in the line of players. Similarly, physicians sometimes think that because there is stagnation in a loop of bowel there must be mechanical obstruction ahead of it. This is not necessarily the case. If the men in the simile were to play in a lane between two board fences, a slowing of the progress of the ball would not mean necessarily that the lane had been narrowed or closed. As likely as not some of the players might be fighting back too hard or those above might not be pushing down as energetically as usual.

Some may be surprised at the idea of one part of the bowel resisting the propulsive efforts of another part above,

but this phenomenon has been observed by so many people besides myself that I feel no doubt about it.

Dietary Suggestions. Some may ask: In what way does the idea of a gradient altered by disease influence our methods of treatment? The answer is that so far little has been done because therapeutists have not been thinking along these lines. Later we may be able to get drugs which will help in restoring the normal gradient, perhaps as calomel does but without unpleasant by-effects. In the meantime there is a diet which is very helpful, probably because it does not lead to conflicts with disordered gradients. Years ago I became impressed with the fact that many of the patients who complained of flatulence and intestinal unrest were passing stools which were full of lumps and undigested material, consisting mainly of cellulose. I found, also, that if I could remove much of this cellulose from their diets they would often get great relief; and the digestion of starches, as shown by the stool examination, would greatly improve. It seemed to me then that the virtues of the smooth diet were to be ascribed mainly to its freedom from a substance—cellulose—for the solution of which the body has no ferment. In recent years it has occurred to me that this diet might give relief to the digestive tract in still another way. Remembering the experiment described in Chapter V in which reversed segments of small intestine were shown to transmit fluids but not solids, it seemed to me that an individual with a good steep gradient might be able to handle any amount of coarse and indigestible material, while a person with a poor gradient or one which is somewhat upset in places would be unable to do so. Such an individual should avoid eating coarse food for much the same reason that he should avoid putting paper, sticks and cotton down a drain

which has a poor drop and several narrow bends. At any rate, whatever the reason, this diet has certainly proved in actual practice to be of great value whenever there is a slight tendency to reverse peristalsis or to a narrowing of the lumen of the bowel. Thus it is useful postoperatively when suture lines or segments of bowel are still irritable; and it is absolutely essential in mild intestinal obstruction, as with carcinoma of the bowel.

The following is the list which I give to my patients:

SMOOTH DIET LIST

Choose from the following:

Breakfast

Orange juice; grape fruit (avoid the fiber).

Cantaloupe and melons are inadvisable as they tend to regurgitate for hours.

Coffee in moderation; chocolate; cocoa or tea.

One or two eggs with ham or bacon (avoid the purely fibrous part).

White bread and butter; toast or zwiebach.

Any smooth mush, such as farina; germea; cream of wheat; cornmeal or strained rolled oats.

Puffed cereals and corn flakes are also allowed.

Shredded wheat biscuits and other coarse breakfast foods are *not* allowed.

Lunch or Dinner

Broths; bouillon; cream soups; chowder.

Small portion of meat, fish, oysters, chicken or squab (avoid the fibrous parts and gristle).

No smoked or canned fishes, or pork.

Avoid veal, crab and lobster if they seem to cause indigestion.

White bread and butter; hot biscuits made small so as to consist mainly of crust. No rough branny breads or bran biscuits.

Rice; potatoes—baked, mashed, hashed-brown or French-fried; sweet potatoes; hominy; tomatoes stewed, strained and with cracker crumbs; well cooked cauliflower tops with cream sauce; and asparagus tips. Later may try brussels sprouts. Italian pastes; noodles, macaroni or spaghetti, cooked soft with a little cheese or cream sauce.

Purees of peas; beans; lentils; lima beans or artichoke hearts. All skins or fiber should be removed by passing through a ricer. "Cornlet" in cans furnishes sweet corn without the indigestible husks. There are practically no other vegetables that can be pureéd to advantage. Spinach often causes trouble and is not recommended. Bananas can be fried in butter or baked in their skins. String beans are allowed if young and tender. No salads at first. Later you may try a little tender lettuce with apples or bananas, tomato jelly or boiled egg. Mayonnaise and French dressing are allowed.

For Dessert

Simple puddings, custards, ice-cream, jello, plain cake, canned or stewed fruit. Avoid cheese, nuts and raisins.

If constipated, stewed fruit may be taken once or twice a day. In winter, the dried pared fruit may be used for stewing. Too much sugar should not be added. Apple sauce is much more palatable if made from unpared and uncored apples. The sauce is strained later. It may be diluted with a little tapioca or sago. The apples may be baked. Blackberries and loganberries can be stewed and strained, and the sweetened juice thickened with cornstarch. This makes a delicious dish with the full flavor of the berries. Canned fruits, such as pears and peaches, are allowed. Later you may try a fully ripe pear, peach or apple.

Avoid most of the green vegetables, salads and raw fruits.

Avoid sugar in concentrated form; take no candy or other food between meals.

Avoid eating in a rush or when mentally distraught.

Objections may be made that such a diet will lead promptly to constipation, but practically it has rarely done so, and in a number of cases it has actually relieved constipation.

Chapter X

REVERSE PERISTALSIS AND ITS SYMPTOMS

IT can easily be shown that most of the symptoms of gastro-intestinal disease are due to disturbances in the mechanical functions. Thus, the great obstacle to the making of an early diagnosis of cancer of the stomach is the fact that the mucous membrane and the gastric secretion may be almost entirely gone and yet the patient may have no symptoms. These arise only when the growth becomes large enough to block the pylorus, and even after that, they may disappear entirely when a channel sloughs through the tumor. As Taylor[423] has aptly said, we seem to have duplicate plants for chemical digestion, but we have only one muscular tube for the motor transport of food. Naturally, when that breaks down we are very promptly apprised of the fact. As we undoubtedly get symptoms when the transport is slowed or stopped, it seems to me that we must get them also when it is reversed. I might add that we get very definite sensations from the bowel also when the transport is speeded. In a sensitive person the peristaltic rushes which usher in an attack of diarrhea may be very distressing. They produce a peculiar sinking feeling in the epigastrium which may be accompanied by chills, cold sweats, pallor of the skin and even fainting.

Now it has been shown in the preceding chapter that the reverse transport of food in the tract is not uncommon. In some places it is physiologic. We know that the duodenal contents regurgitate into the stomach. We know that there

is reverse peristalsis in the upper half of the colon; and all of us are acquainted with the phenomena of belching, regurgitation and vomiting. Since the time of Hippocrates, physicians have commented upon the fecal vomiting of ileus; and there are innumerable well authenticated instances in which people have vomited enemas and suppositories (Schloffer,[388] Langmann,[251] Weber[441]). A review of the literature shows a surprising number of cases in which these observations caused surgeons to operate for a gastrocolic fistula which was not found (Treves[433]). I have talked with a number of intelligent persons who objected to their nutrient enemas because they were regurgitating some of the material, and did not like its bitter taste. Doctor Emge of San Francisco tells me that after severe pelvic operations it is his custom to give enemas of coffee which not infrequently can be detected in the vomited material. At first he thought it was dark blood, but a chemical examination showed that it was coffee.

It is well known that in most instances barium enemas flow back into the ileum and that occasionally the material will reach the duodenum (Quimby,[367] p. 403). I have seen liquid and gas pass rapidly from the colon to the duodenum in cats. The animals were anesthetized and their abdomens opened under salt solution. The rectum was tied off and the colon filled with air or thick soup. After that part of the bowel had become very irritable and highly tonic through its efforts at emptying, some of the material was rushed well up into the small intestine.

Granting, then, that the possibility of reverse transport of food through the tract is well established, the next question is: Are there mild forms in which perhaps the gradient is simply flattened, or in which there are ripples travelling up the bowel, and do these ripples cause symptoms?

Do they affect the consciousness of the individual and if so, how? In the following paragraphs I wish to discuss a few symptoms which are often found together or alternating one with the other in the same patient, and which I believe indicate such mild reverse peristalsis. These symptoms are vomiting, regurgitation, heart-burn, belching, nausea, socalled biliousness, coated tongue, some types of foul breath, a feeling of fulness immediately after beginning a meal, globus and possibly at times, hiccup (Alvarez[9]). In taking a history, these symptoms should be inquired into very carefully because if the patient has a lesion anywhere along his tract sufficiently irritable to alter the gradient, he should have some of these manifestations. If, on the other hand, he complains only of a little flatulence with some discomfort or vague pain one must be slow to make the diagnosis of an organic lesion.

(1) VOMITING. The act of vomiting is accomplished with the help of a center in the medulla which coordinates the movements of the voluntary muscles with those of the digestive tract. Unfortunately, so many even of the physiologists have been obsessed with the idea that the stomach is the organ of digestion that very few of them have paid any attention to the behavior of the intestine during vomiting. I believe that a little more careful observation would show that in many cases the bowel does play a considerable part, perhaps not so much in the act of vomiting itself, but in the preparation for it. Thus, on some occasions, while watching the contractons of the intestine in animals opened under salt solution, I was struck by the fact that violent contractions in the jejunum were followed a few seconds later by the regurgitation of material through the mouth. I have graphic records from the intestines of cats, and also

from a man with a jejunal fistula, showing that a marked rise in the tone of the upper bowel preceded vomiting. Less convincing observations were made on a child with severe recurrent vomiting, in whom the attacks were preceded by violent intestinal peristalsis and borborygmus loud enough to be heard several feet away.

A review of the literature shows that a few writers have made similar observations. Openchowski,[345] in describing vomiting, speaks of a preliminary increase in the activity of the bowel; and Boldireff[63] (p. 489), one of the best of the Russian observers, noticed during some experiments that periods of intestinal activity were sometimes accompanied by vomiting. Such activity tends to force intestinal contents back into the stomach. I have been able to confirm Ewald's[144] statement that in ileus the stomach is filled with such regurgitated material for some time before fecal vomiting appears. If long stretches of bowel are operatively reversed in dogs so that the current is directed backward towards the stomach, the animals will vomit unless fed very carefully (Kelling,[233] p. 326). Von Bechterew and Weinberg[43] (p. 259) say that curarized animals which cannot vomit will regurgitate when given certain emetics.

Physicians seem to think sometimes, because they find so much bile in the vomitus, that it is producing the emesis. It has been well proved that that is not so, because the duodenum has been closed off in dogs and in man so that all the secretions of the liver and pancreas had to go through the stomach on their way into the jejunum (through a gastro-enterostomy) and yet there was no vomiting (Chlumski,[114] Rosenberg,[377] Ledderhose,[257] Moynihan,[329] Kölbing,[239] Wiedemann[446]). Hence it seems to me that when, as commonly happens, we find large amounts of bile-stained fluid in a stomach which has been emptied a few minutes

before, we can be sure that it has come from the bowel, and that the same cause which is producing the back-flow is producing the vomiting.

Physicians often think that they can stop vomiting if only they can keep food out of the *stomach*. They forget that vomiting is often very severe with lesions far down in the bowel and that it may be entirely lacking in serious gastric disease, such as ulcer and carcinoma, without pronounced pyloric obstruction (Faulhaber and von Redwitz,[148] p. 680). Cohnheim and Dreyfus[117] (p. 56) produced vomiting in dogs by distending balloons in the intestine. They found that a slowing of gastric emptying could easily be effected by irritating the bowel, whereas it was not observed after the production of a severe gastritis. Hirsch[189] (p. 380) produced vomiting in dogs by giving solutions of organic acids. Acetic acid was most effective, apparently because it had the least action on the stomach and the most marked stimulating effect on the intestine. The regurgitation of bile-stained contents into the stomach showed that the gradient was upset. Lactic acid, which had less effect on the gradient, produced only a delay in gastric emptying.

As is well known, vomiting is often observed in pregnancy, particularly during the first few months. Obstetricians generally distinguish between the milder cases in which the cause is said to be "reflex," and the severer ones in which the cause is probably a toxemia. I have been impressed by the fact that nausea and vomiting very similar to that in pregnancy is observed in women whose pelvic organs are kept irritated, inflamed or abnormally hyperemic by unsatisfactory suspension operations; by fibroids, pus-tubes or diseased ovaries. These lesions keep the uterus in much the same condition as it is in the first few months of pregnancy; and the symptoms disappear immediately after the oper-

ative removal of the source of irritation. It has occurred to me that the increased activity and vascularization of the uterus in pregnancy and with these inflammations might in some way raise the tone and irritability of the lower part of the bowel, and thus reverse the gradient. So far I have been able to study the gradient in only a few pregnant animals. In most of these there was little change shown in the rhythmicity of the excised segments; and it is only suggestive that in a few animals studied with the abdomen open under salt solution the rhythmic gradient was markedly flattened by an increase in the rate of the ileum. That the gradient in pregnant women is flattened is suggested not only by the vomiting but by the regurgitation of acid gastric contents into the mouth. Some women will suffer during one pregnancy from vomiting and during another from severe heart-burn.

It is possible that the lower bowel shares in the hyperemia of the pelvic organs. There may also be a spread of "tone" along the pelvic nerves. Elliott and Barclay Smith[138] (p. 282) found that stimulation of these nerves will raise the tone of the midregion of the colon and will increase the tendency to reverse peristalsis there. Quite a few women notice a tendency to diarrhea on the first day of menstruation, and there again we have evidence of some effect transmitted from the hyperemic uterus to the bowel. The fact that a uterine hyperemia from any cause may upset the intestinal gradient makes me feel that the action in pregnancy must often be direct and not by way of any toxemia.

The tendency to reverse peristalsis in pregnancy was well recognized years ago by Campbell.[79] He states clearly that the woman with pregnancy or pelvic disease has an irritable tract in which "response is usually by inverted rather than

by direct action: eructation, regurgitation, nausea, vomiting, constipation, far more frequently than diarrhea and other manifestations of downward action. The tract gets into the habit of retrostalsis." The stormy vomiting and dynamic ileus seen sometimes after pelvic operations may be due to a great and sudden increase in the irritability of the colon. One may perhaps explain also in this way the vomiting seen sometimes after injury to the testicle (Müller,[336] p. 37). Upsets in digestion may be produced also in men by enlarged prostates and distended bladders (Peyer,[359] p. 3182; Herschell,[186] Hutchison,[206] p. 485; Stockton,[413] p. 129; Austin,[26] p. 52). These seem to correspond closely with those observed in women with inflamed and gravid pelvic organs. Many will say that these things are purely "reflex," but that word does not help us very much; and I think we are justified in looking for a simpler and better explanation.

Vomiting can sometimes be stopped by giving solid food which may act perhaps by raising the tone of the stomach and restoring the downward gradient. Liquids often fail to stop vomiting, perhaps because they tend to run directly into the intestine without affecting the stomach very much.

(2) REGURGITATION. In true vomiting, the return of the gastric contents into the mouth is effected mainly by contractions of the voluntary muscles in the abdomen and thorax; in regurgitation, it is effected mainly or solely by contractions in the smooth muscle of the stomach, bowel and esophagus. There are, however, many grades or stages between the two—between the projectile vomiting in cases of brain tumor, and the half vomiting, half regurgitation often seen in infants and in hysterical girls. Furthermore, a woman with, let us say, an irritable gall-bladder may regurgitate during some of her attacks and vomit in others.

Regurgitation is commonly observed even in people with good digestions, if they eat certain foods like onions, musk-melons, bananas or fats. They can taste these foods at intervals for hours after they are eaten. The fats probably act in this way because while they depress the gastric activity (von Tabora,[420] Cannon,[83] p. 315), they stimulate that of the bowel, and thus increase the normal tendency to duodenal regurgitation (Babkin,[28] Lintwarew[269]). It has often struck me as suggestive that those foods which cause regurgitation when eaten in small amounts may cause vomiting when eaten in large amounts. Furthermore, some of them produce heart-burn in some people; and we shall see later that that is due probably to the regurgitation of the gastric juice into the pharynx.

Some women regurgitate at the beginning of the menstrual period; others have a great deal of trouble with it during pregnancy. The fact that troublesome regurgitation may cease a few minutes after the patient has a bowel movement suggests strongly that the distension of the pelvic colon can keep that region overactive and can cause it to give off reverse waves. These waves need not be so powerful that they sweep material along before them. I have commented elsewhere on the fact that in the rabbit's intestine peristaltic rushes here and there can be shown by graphic records to have originated in ripples which have come, unnoticed by the naked eye, all the way from the pylorus (Alvarez[3]). It seems to me probable that ripples coming from a full or overactive colon, or from the irritable ileocecal region in subacute appendicitis can run up the bowel and show themselves in the stomach and esophagus as waves of acid regurgitation. Smith and Lewald[403] (p. 271) have commented upon the frequency with which regurgitation accompanies colic in children. It is probable that the waves causing this

regurgitation arise in the overactive part of the bowel. The following case is very suggestive: A constipated infant regurgitated so much every day that her pillow was always soaked. After weeks of this her bowels suddenly became a little loose; and the day on which this occurred the mother was surprised to find the pillow perfectly dry. It remained that way for over a week until the bowels became constipated again. Apparently the establishment of a good current downward instantly stopped all regurgitation upward. Hippocrates seems to have had very similar ideas about the gradient, because he says: "In confirmed diarrhea, vomiting, when it comes on spontaneously, removes the diarrhea[188]." I have seen exactly that thing happen in cases of tuberculosis of the cecum.

(3) HEART-BURN. Before giving my views as to what heart-burn is I must emphasize what it is not. Practically every one who has studied the subject has agreed that only a small proportion of the patients complaining of sour stomach or heart-burn have an actual increase in their gastric acidity (Schütz,[393] Steele,[409] Stockton,[413] p. 157). Titration of the burning fluid that has been regurgitated often shows subacidity; and gastric analyses made during the periods of discomfort do not show values any higher than those found during periods of relief. Furthermore, all of those who have put from 0.5 to 2.0 per cent hydrochloric acid by tube into the human stomach agree that their subjects could hardly perceive it (Hurst,[200] p. 101; Ginsburg, Tumpowsky and Hamburger,[166] Carlson and Braafladt,[97] p. 163; Zimmermann,[455] Löwenthal,[274] Schür,[392] Schmidt[389]). At most there is a slight sensation of warmth. A number of writers have felt that they could explain away the difficulty by saying that the *diseased* stomach is so hyperesthetic that

it can feel the acid. This idea has been discredited by the work of Hurst[201] (p. 12), Löwenthal,[274] and Schür,[392] who showed that persons with ulcer, demonstrated later at operation, could not feel the acid any more than normal persons can. Other explanations for the appearance of heart-burn have been offered, but it seems to me the true one is that given by Reichmann,[374] thirty-seven years ago. He had people swallow a little gelatin-coated sponge on the end of a string. After leaving it for ten minutes in the lower esophagus, he pulled it out, squeezed it, and found that the fluid expressed was acid in the persons who had heart-burn, and alkaline in normal controls. He concluded, therefore, that heartburn was due to a regurgitation of gastric juice. This view has been held independently by a number of men, but some doubt has been cast upon it by the work of Hurst,[201] (p. 12) who states that the esophagus is not sensitive to acid. This is not true for all people. Those who have prescribed hydrochloric acid in cases of achylia gastrica know that some people complain of its burning them and others do not. I have experienced severe and typical heart-burn after drinking a solution of acidol, a drug which liberates hydrochloric acid when dissolved in water. The lower pharynx is probably more sensitive to the acid than is the rest of the esophagus, and many people say they feel the heart-burn in the back of the throat. One cannot be sure about that localization, however, because it is known that sensations derived from the esophagus between the clavicle and nipple may be referred either upward into the throat or downward into the epigastrium (Boring,[65] p. 34). Some intelligent people who have suffered greatly from heart-burn have told me that their dentists have found that the enamel was badly eaten off of their back teeth; and I believe some one has suggested that regurgitation of acid juice may be one of the

causes for that deterioration of the teeth which is so often seen in pregnant women.

Some nervous women complain at times of a burning feeling in the epigastrium, as if the stomach were "on fire." This seems to be an entirely different thing. The fact that it sometimes moves to the lower part of the abdomen or down on to the thigh shows that it is a paresthesia which has nothing to do with the stomach.

One of the most suggestive things about true heart-burn is its well known association with belching and regurgitation. Many say that they feel the burning only when the fluid comes up. Occasionally it is worse when they are lying down, perhaps because the gastric juice can then more easily run back up the esophagus. It is often brought on by eating fats which, as is well known, tend to regurgitate. Some men suffer from heart-burn after using tobacco. Perhaps in the habituè, regurgitation of gastric juice takes the place of the nausea and vomiting of the neophyte. Similarly, in a few sensitive individuals small doses of digitalis cause heart-burn whereas, as is well known, in large doses it produces vomiting.

If people with heart-burn ordinarily have no increase of gastric acidity, why are they so often relieved temporarily by the taking of alkalies? It seems to me that this may do good in several ways: First, by neutralizing the acid in the stomach; secondly, by enabling the person to belch so noisily and satisfactorily that he does not feel like doing it again for some time; and thirdly, perhaps, by quieting the contractions of the stomach.

If heart-burn is due to regurgitation of gastric contents into the esophagus, why is it that the fluid that comes up sometimes tastes fresh and sweet while at other times, in the same person, it is intensely acid and bitter? It is now well known that there are three parts of the stomach: (1) the

fundus, which holds the food fairly motionless, often in layers as it comes in; (2) the muscular antrum, which breaks the food up and mixes it with the gastric juice; and (3) the canalis gastricus which carries fluids along the lesser curvature and out into the duodenum. It seems to me that the regurgitated food that tastes fresh has probably come from the top of the pile in the fundus, the burning liquid has come from the antrum or even from the duodenum, and has probably travelled up the gastric canal. Schilling[387] found that the regurgitated fluid was alkaline in some people, and in one case he though it was pure duodenal juice.

Heart-burn is often very severe and trying in pregnancy where it may take the place of vomiting. Some women will have vomiting with one pregnancy and severe heart-burn with another. It is present sometimes on the first day of menstruation. It may be a pronounced symptom with certain pelvic diseases and also at the menopause. In many of the older women, however, it must be admitted that the reverse waves may be arising in a diseased gall-bladder. Heart-burn is often a marked symptom in chronic appendicitis, in duodenal ulcer, and in gall-bladder disease. In all of these conditions I think it represents reverse peristalsis arising near the lesion.

(4) Belching. We may first distinguish three types: (1) a gurgling sensation or sound which seems to run up the esophagus, and perhaps out along the eustachian tubes; (2) involuntary regurgitation of gas from the stomach; and (3) a voluntary swallowing and expulsion of air. This air ordinarily descends only into the middle or lower esophagus, but occasionally some of it is forced into the stomach (Kantor[225]). I often tell these people that they are simply scratching themselves with the air. Often, as with scratch-

ing, the more the victim does the more he wants to do, so that the quickest way in which to get relief is to desist until the desire has passed off.

Although many of these patients are neurotic and are suffering from a bad habit, I believe that many of them actually have some organic lesion which is sending off reverse waves, is making them uncomfortable, and is giving them the desire to belch. It is remarkable the amount of relief that they get sometimes by taking a little sodium bicarbonate. A man will wake up about two in the morning with great distress; for an hour he may walk the floor, rubbing his abdomen and trying to belch. Finally, after taking some soda, he belches noisily; perhaps he vomits a little bile and water, and within a few minutes he is comfortable and falls asleep. The relief obtained is so out of proportion to the amount of air or liquid expelled that it seems to me that it must be due to a quieting down of the tract after the reverse waves have succeeded in running out. I can only compare it to the tremendous mental and physical relief that comes to a sensitive person when he reaches the toilet after he has restrained a rectum full of gas for hours at some public gathering. The violent peristaltic contractions cease instantly and the whole nervous system quiets down.

(5) Nausea. It is well known that nausea ordinarily precedes or accompanies vomiting. It seems to me very probable that it is brought about by reverse peristalsis, particularly in the bowel. It apparently is not produced by lesions of the stomach alone because it is often entirely absent with extensive carcinomas of the organ, and it is not a prominent symptom of gastric ulcer. It is much more common in acute and subacute appendicitis and in other

inflammations of the lower bowel. As is well known, it is very severe in pregnancy and in other disturbances of the pelvic organs. It is often marked in hysterical women who show other signs of reverse peristalsis. More rarely, it is observed in men with large prostates and distended bladders. I have seen it as the first and for months the only symptoms of carcinoma of the colon but I have never seen it with esophageal disease or with regurgitation due to cardiospasm. Dogs appear to be nauseated when irritant solutions are injected through fistulae into their upper bowels; and we know that these substances regurgitate into the stomach (Cohnheim and Dreyfus,[117] p. 2484).

Patients suffering from nausea sometimes describe it as coming in ascending waves, and I have noticed the same thing myself. It has made me wonder if possibly I was feeling actual reverse waves in the bowel. When I am nauseated, the distress is lessened by lying on the right side and is made much worse by lying on the left. Other people have told me the same thing; but some think their nausea is worse when they lie on the right. These observations suggest that the sensation is affected by the position of the gastric contents. Nausea may be produced also by pulling on the mesentery during abdominal operations under local anesthesia (Farr[147]). Barclay,[31] believes that nausea is associated in man with a drop in gastric tone.

The nausea caused by disgusting mental impressions; by rolling movements, as at sea and by cerebral and aural disease, might conceivably be due to a reversal of the gradient in the upper part of the tract, brought about by an unequal or dissimilar action of the vagus on different parts of the stomach and bowel. This possibility has been discussed in the preceding chapter. It is an interesting point that in many cases of vomiting due to brain lesions

there is no preliminary nausea. This observation agrees with the others in suggesting that the sensation of nausea is produced in the bowel and not in the brain. If this reasoning is valid, it can be used as an argument in favor of the view that some emetics tend to reverse the gradient in the bowel because, in small doses, they produce nausea without vomiting. It would be an interesting experiment to see whether people whose vagi have been cut across, as in complete gastric resection, can experience nausea after taking emetics, or during spontaneous vomiting.

Some people experience nausea when constipated and are relieved immediately after emptying the rectum. Others are nauseated after taking enemas, particularly if those enemas contain irritant substances. A few people feel nauseated also when they are hungry, and get relief immediately after taking food. That probably restores the downward gradient.

(6) Coated Tongue and Foul Breath. It is commonly supposed that the tongue in some sympathetic way reflects the condition of the gastric mucous membrane. I can find, however, no proof of any kind for this view. It seems to be based on the idea that many gastro-intestinal upsets are due to, or associated with a gastritis. The recent more careful study of stomachs which have been filled with formalin solution immediately after death, and the work done on sections removed at operations have shown that gastritis is a rather rare disease (Beitzke[45]). About the only place in which it is found is in the neighborhood of large gastric ulcers, carcinomatous and benign. It would seem now to be a poor diagnosis to make even in alcoholics. Hirsch,[190] has shown that true inflammatory changes are hard to demonstrate even in the stomachs of patients dying from delirium tremens.

By far the best explanation for the coated tongue has been given by Kast.[224] He gave lycopodium powder in sealed capsules to a number of persons, and was able to recover the typical spores in the mouths of most of them the next morning. I have had no difficulty in confirming these experiments. In one case, that of a woman who regurgitates a good deal, particularly during the menstrual period, the tongue became yellow from the lycopodium.

It is possible that some of the particles making up the coat of the tongue may come from even below the stomach. Grützner[172] and also,[173] and others (Swiezynski,[418] Reach,[371] Hemmeter,[184] Bernheim,[50]) have shown in animals and in men that lycopodium spores, or other finely divided and easily recognizable material given in enemas will travel in a few hours from the rectum to the stomach. Similarly, Uffenheimer,[436] Dieterlen[127] and others found that bacillus prodigiosus injected into the rectum could be recovered from the pharynx a few hours afterwards, when every precaution had been taken to prevent the animals from licking themselves or from touching their feces. Transmission through the blood stream was pretty well ruled out. In cases of pelvic peritonitis with intestinal obstruction, I have seen a brown coating on the tongue with a typical fecal odor long before fecal vomiting appeared. Hence it seems to me most probable that many of the coated tongues which we see are due to the regurgitation of gastric and intestinal contents, especially during the night. This view is strengthened by the fact that the coating is often heaviest at those times when belching, regurgitation and the feeling of "biliousness" are most pronounced.

Laymen and physicians often feel that the bad breath, coated tongue and bad taste in the mouth with constipation are due to the exhalation of absorbed toxins which have

come through the blood. I have given elsewhere my reasons for putting little faith in these theories of auto-intoxication (Alvarez[19]). The bad breaths of people with diabetes and nephritis, or of people who are dying may be due to exhaled substances, but I think the mechanism is quite different in constipation. There it seems more probable that the odor comes from actual intestinal material deposited on the back of the tongue. I need hardly say that the reverse currents must not be blamed for every coated tongue. There are other factors often present in the nose, mouth, pharynx and salivary glands which must be studied in individual cases.

(7) Feeling of Fullness After Beginning to Eat. In rare cases this may be due to an actual shrinkage in the capacity of the stomach following ulceration of various kinds, but ordinarily the roentgen ray examination will show a normal or even a dilated stomach (Leven and Barrett,[261] p. 142; personal observations). Sometimes the patient ascribes his feeling of fullness to the presence of gas, but again, a careful examination often shows that he is mistaken. Carlson[96] (p. 111) has shown moreover, that these sensations do not arise in the gastric mucous membrane. Hurst[201] (pp. 22 and 28) found that they may arise if the intestine is distended too rapidly by food coming through a gastro-enterostomy opening; and I have seen the same thing during jejunal feeding. It seems to me very suggestive that these sensations are often associated with other signs of back pressure. Sometimes this pressure is so strong that the patient can hardly swallow. He says that the food does not seem to want to go down, or that he feels as if something met it and pushed it back. That apparently is one of nature's methods of telling us that the gradient is reversed and that the tract is not prepared to receive food. The intensity of

this feeling in some instances is well shown in a case described in Chapter XI.

(8) GLOBUS. A few times in my life I have happened to swallow while a wave of regurgitation was on its way up the esophagus, and when the two waves met there was a painful tearing feeling. It may be that globus is brought about somewhat in that way (Marshall Hall[177]). Some patients describe it as a lump moving up and down the esophagus, and it is suggestive that the hysterical, who are supposed to suffer most from globus, sometimes present the most striking manifestations of reverse peristalsis.

(9) HICCUP. There is no doubt that under certain conditions of diaphragmatic irritability, involuntary belchings of gas or waves of esophageal regurgitation will be followed immediately by a spasmodic contraction of hiccup. Similar contractions will sometimes be excited by swallowing. In these cases it seems likely that the diaphragm is stimulated either by a sudden distension of the fibers around the esophageal opening or else by the action current of the esophageal muscle. The latter theory seems not improbable because the diaphragm has been observed to twitch rhythmically under the stimulus of the action current of the heart. It is suggestive that hiccup is not infrequently a troublesome symptom after serious operations when the gastro-intestinal currents are plainly reversed. Other factors are undoubtedly at work, and there probably are many varieties of hiccup in which reverse peristalsis plays no part.

(10) "BILIOUSNESS." This is often nothing more than the layman's term for the reverse peristalsis syndrome. Certainly, few thinking physicians to-day would ascribe

that group of symptoms to hepatic insufficiency, although they are often seen with definite gallbladder disease. More often the reverse waves seem to be due purely to the stagnation of the colonic contents in constipation. Biliousness derives its name probably from the fact that the sufferers note bile in the regurgitated or vomited material. As the presence of bile in the stomach is normal, any excess need not indicate disease of the liver so much as an increase in the normal duodenal regurgitation. Many of these people are found at operation to have actual organic disease like cholecystitis or chronic appendicitis; others, whose attacks are ushered in by violent headaches have, I believe, a hereditary brain disease; a sort of sensory epilepsy. Some irritable area in the brain seems to send a "storm" down the vagus which upsets the intestinal gradient much as it is upset in seasickness or Ménière's disease. In a number of cases I have seen the severity of the symptoms and perhaps the number of attacks diminished after the removal of a diseased gallbladder or appendix, but a little fatigue could still bring on a typical headache.

The relief which these people derive from purgation, and particularly purgation by calomel is due not to any action on the liver (for all pharmacologists are agreed that there is no cholagogue action), but, I believe, to a restoration of the downward current. The relief comes so promptly after the evacuation of the bowel that I am sure it cannot be due to the removal of a source of toxins (Alvarez,[19] p. 12). If the symptoms were due to circulating poisons they would have to wear off gradually like those of an alcoholic debauch.

Those who may feel that I have appropriated too many of the gastro-intestinal symptoms for this syndrome should remember what I said at the beginning of this chapter.

If, as seems likely, symptoms are produced almost entirely by disturbances in motor functions, we should be most conscious of, and most annoyed by, the severest possible form of such disturbance, namely, a reversal of the current. In other words, many or most of the sensations which reach our sensoriums when digestion is disturbed, should be those originating in reverse peristalsis.

Chapter XI

OBJECTIONS AND DIFFICULTIES

As I stated in the Introduction, the first question that bothers many clinicians is: What relation have my ideas on peristalsis to the current theories about *vagotonia and sympathicotonia?* Many men are satisfied that these two magic words explain everything; but their views are often so hazy that they cannot be sure whether my findings require new mental adjustments on their part or not. Similarly, one finds the author of a recent textbook quoting in one breath the "beautiful work of Gaskell and Eppinger and Hess," apparently quite oblivious to the fact that the one spent most of his life gathering exact data which knock the supports out from under the theorizing of the other two. It seemed well, therefore, to review briefly the function of the extrinsic nerves of the digestive tract. After having to emphasize so strongly the autonomy of the tract and the importance of local muscular mechanisms, it is well to point out that there are extrinsic nerves and that they have functions. Before saying what these functions are I must say what they are not.

The Extrinsic Nerves of the Digestive Tract. The usual statement found in textbooks is that the autonomic (vagi and sacral nerves) stimulate, and the sympathetic fibers inhibit the intestine. Disease is supposed to follow an unbalance between these two effects. This unbalance can be diagnosed and corrected by the use of certain drugs which

are supposed to be elective in their actions. These theories of vagotonia and sympathicotonia have had a strange fascination for the medical mind; they have been dragged in with the utmost assurance to explain all sorts of disease states, and I believe have had a most unfortunate influence on our conceptions of gastro-intestinal physiology. It may be that these theories will eventually prove useful, but in my opinion their foundations are so shaky that some day the whole edifice is going to go. In the following brief discussion I can only point out a few places in which the proponents of these theories have made things much simpler than they really are.

Although in the main, the vagus tends to stimulate and the sympathetic to inhibit the stomach and bowel, these effects are generally transient; often indecisive, and not infrequently reversed (Cannon,[86] p. 198; May,[302] Kelling,[234] Weil[443]). They vary with the strength of the stimulus and with the condition of the muscle. The first effect of vagus stimulation is generally a lowering of the tone. After from fifteen to sixty seconds there may be an increase of tone and activity which lasts a few seconds or minutes and then disappears. Spadolini[406] (also[407]) has shown recently that one can get purely inhibitory effects by stimulating the vagus, and purely augmentor effects by stimulating the splanchnics. Opposite effects can be obtained in different parts of the gut from one and the same stimulus. Weak currents tend to inhibit while strong ones stimulate. According to Bercovitz and Rogers,[48] a tetanizing current stimulates and an interrupted one inhibits. Bunch[77] found that splanchnic stimulation inhibits in the cat but generally augments the movements in the dog.

Another difficulty with the vagotonic theories is that the vagus is not a simple nerve like the motor roots supplying

the voluntary muscles of a frog. It is a plexus: a bundle of nerves of all sorts and sizes, medullated and non-medullated (Chase,[109] Barratt,[36] Edgeworth[132]). Most of the fibers probably are connector neurones running from the brain to motor ganglia in Auerbach's plexus; but there are also afferent or sensory neurones, and even some sympathetic fibers (Miller,[320] Neumann[341]). Similarly, a "sympathetic" nerve in the abdomen may consist of pre- and post-ganglionic fibers, fibers to muscles, fibers to blood vessels and glands, and even sensory fibers belonging to the central nervous system. We generally lose sight of the fact, too, that the effect of a strong—often a traumatizing or damaging—electric shock is not necessarily the same as, or even comparable with the effects produced by the normal, more or less continuous stimuli which come from the brain or from the sensory side of the reflex arcs. For this reason I think we have much to learn yet about the functions of the visceral nerves.

One of the strongest objections to the recent theories in regard to the autonomic and sympathetic systems is that they make it appear that the sympathetic nerves with the celiac ganglia constitute a separate and distinct brain system which can be antagonistic to, or out of harmony with the central nervous system. This view is entirely at variance with the facts which have been collected and discussed in a masterly way by Gaskell in his monograph on "The Involuntary Nervous System."[160] He shows that the involuntary nerves and ganglia are a part of the central nervous system; that they are connected with it just as the voluntary nerves are, and that they have developed from the same embryonic cells (Abel[1]). The main difference is simply that the motor ganglia which in the voluntary system are found in the anterior horns of the cord, have migrated; some as far as the paravertebral ganglionic chain; some into the solar

plexus, and some into the nerve nets in the walls of the hollow organs. Hence it is that the rami communicantes or preganglionic fibers in the sympathetic system, and most of the efferent fibers in the vagus are simply elongated connector neurones such as we find between the motor and sensory roots in the cord, and in the pyramidal tracts. Furthermore, it has been shown that there are no commissural fibers between the different sets of sympathetic ganglia such as would have to be present if these ganglia were to mediate reflexes like an abdominal brain (Johnson,[217] Langley,[248] Carpenter and Conel[102]). Actually we find that the movements in the involuntary muscles connected with these ganglia "are essentially movements *en masse*, and not delicately coordinated movements, such as are so characteristic of the voluntary system." We see, then, that the *involuntary system is simply a part of the voluntary system* characterized by the outward migration of the motor ganglia and the necessary lengthening of the connector neurones. On the sensory side there is no difference between the afferent fibers in a sympathetic nerve and those in a spinal nerve—they both go to the posterior root ganglion in the cord (Langley,[249] p. 17).

We learn, then, from Gaskell the same lesson that we have had from Loeb and from Parker: that the nerves are there to conduct, and not to exercise faculties requiring almost human intelligence. There are times when the animal as a whole needs to communicate with its digestive tract; there are times also when the tract must communicate with the body. There are many times when one end of the tract must communicate with the other; and on all these occasions the extrinsic nerves come into play. The vagi carry feelings of hunger and of satiety from the stomach to the brain (Cohn[115]); they help in adjusting the tone of the stomach wall to the

food coming down the esophagus (Cannon,[86] p. 200); and they carrry the stimuli that give rise to the psychic secretion of gastric juice. If the food must be rejected by vomiting, they carry the impulses which bring the abdominal muscles to the aid of the stomach. Moreover, they probably carry messages from the digestive tract which make the animal feel comfortable and sleepy (Loeb,[270] p. 96). The splanchnics serve largely to quiet the tract and to stop digestion when the body is distressed or injured (Cannon,[85] p. 480). The extrinsic nerves probably have much to do with the digestive upsets with disease elsewhere in the body, but we saw in Chapter IX that these changes can be accounted for also by actual damage to the gastro-intestinal muscle.

The Law of the Intestine. Many have asked: What relation has the gradient idea to the studies of Bayliss and Starling, and Cannon? Do they conflict, or does the gradient idea supersede the others? I think it will be plain to any one who is conversant with the literature on the motor functions of the digestive tract that there is no serious conflict. Careful experimental work remains of value no matter what comes afterwards; but as I have said before, the interpretation based upon that work often changes in the light of additional knowledge. About the only place in which I differ from Bayliss and Starling and Cannon is in the estimate put upon the value of the "Law of the Intestine" or the "Myenteric Reflex."

According to that law (Bayliss and Starling,[39] p. 110), "excitation at any point of the gut excites contraction above and inhibition below," and that "reflex" is supposed to explain easily the downward progress of food. There are so many objections to such a view that it is surprising that no one besides Cannon[90] (p. 125) has called attention to them in the last twenty years. In the first place, the few

who have written about the myenteric reflex all admit that it is hard to demonstrate; that it is often absent and often reversed. Bayliss and Starling point out that the reaction generally takes place within a few centimeters of the stimulated place. The inhibition below is confined mainly to the circular muscle and it is often absent. "In many cases, however, our results have not been quite so clear. Although stimulation above the balloon produced inhibition, stimulation below produced also inhibition or preliminary inhibition followed by contraction." Again: "The two effects do not run absolutely parallel to one another, in that in some experiments the inhibitory effects from above, in others the augmentor effects from below, may be better marked." These troubles persisted even after the extirpation of the abdominal ganglia. In another paper they admit that when they changed from dogs to cats they did not get good pinch reactions (according to the law) until they remembered that they had always given the dogs a preliminary dose of castor oil. Even when they gave this drug to the cats they did not get as typical reactions as they got in the dog. They had difficulties again when they tried to use rabbits for this work. It seems to me that so important a law should be capable of demonstration in all of the laboratory animals without the help of drugs. Moreover, Bayliss and Starling admit that their technic could be objected to because the bowel is not normal when it has been opened so that a balloon and its attached rubber tubing can be put in. My own experiments with balloons greatly impressed me with the abnormal nature of the conditions, and made me feel that I could put little trust in the results obtained.

Magnus[289] (p. 132) says he was able to show the law on excised strips of intestine stimulated with a salt crystal. He admits, however, that he could not obtain the expected

reactions "with mathematical regularity." In some animals he got inhibition above and below. Langley and Magnus[250] (p. 46) also had considerable difficulty in trying to show the law. They say: "It must be noticed that although inhibition below a point stimulated was so frequently obtained, it was in any one experiment, which lasted two to three hours, very inconstant; at one time the inhibition would be marked and at another absent, and the period during which one or the other state supervened was sometimes at the beginning of an experiment, sometimes an hour or two later." Degenerative section of the greatest majority of the superior mesenteric nerves did not abolish the reactions, showing that their mechanism is located in the bowel wall.

Cannon realized fully that the "myenteric reflex," as he called it, is not always demonstrable. "What causes (it) to appear or not when material is present, is as yet undetermined . . . It does not govern the rhythmic contractions of the small intestine, the rhythmic peristalsis and antiperistalsis of the colon, and probably not the rhythmic waves of the stomach." (Cannon,[90] p. 125; and also,[86] p. 195.)

Miss Starkweather and I studied the graphic records of the contractions resulting from over two-thousand stimuli (mechanical, electrical and chemical) applied to the intestine (mainly of rabbits) and found that the usual response in all but about twenty of the experiments was a contraction above and below (Fig. 21). Most of the few responses that corresponded to the law were obtained by distending the bowel with a small balloon. One objection to our experiments is that in most of them the records were taken from the longitudinal muscle, while Bayliss and Starling got their results mainly with the circular. Another objection that can be made to all the work done so far is that the stimuli used are abnormal. What we want to know is how the bowel

behaves above and below a loop-ful of the usual intestinal contents. My own records taken with a number of enterographs show no sign of any descending inhibition in front of small peristaltic rushes (Fig. 3). On the other hand, the bowel ahead of such waves often contracts powerfully so as to keep them from going too far. If it were not for that

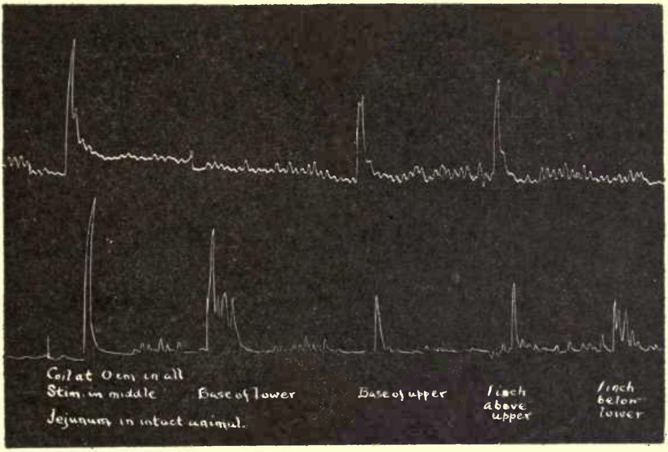

Fig. 21.—A coil of jejunum 8 cm. long in an intact rabbit (abdomen opened under salt solution) was made to record at both ends. When this bowel was stimulated faradically near the upper recording thread it responded below; when it was stimulated near the lower end, it did not respond above. When stimulated midway between, the twitch at the lower end was greater. Note the absence of the myenteric reflex.

mechanism our digestive tracts would promptly be emptied of everything in them.

It seems clear from the foregoing that the law of the intestine needs further study and it needs restatement. Perhaps it is more strictly a response of the circular muscle to distension; and it may be that we can say later why it can be elicited one moment and not the next, or in one

animal and not another. There is much anatomical evidence to show that it is not a "reflex;" that is, the necessary nervous arc can not be demonstrated in the intestinal wall. Gaskell[160] has pointed out that, at most, it may be what is called an axon reflex. Another argument against the "reflex" is that it has not been helpful to the clinician in explaining the peculiarities of peristalsis, particularly in disease. It seems to me that if it were really fundamental it should be exceedingly helpful in practice, much as the gradient theory is helpful.

I believe that the great tendency to contraction at the upper end of a bolus may perhaps be explained on the basis of the gradient. I showed in a previous chapter that smooth muscle, especially when in connection with a nerve net, responds first at the point where the tension or pressure is greatest (von Uexküll[435]). Now, if the tone of the muscle in a tube is everywhere the same—if there is no gradient—and if the bolus is perfectly cylindrical, the distending force will be equal along that bolus and the tendency to contraction will be the same everywhere. There are two ways in which the contractions might be thrown to one end or the other. The bolus might be somewhat conical, in which case the muscle would be more stretched at the end with the greater diameter; or the primary tension or tone of the muscle might be graded, in which case a purely cylindrical bolus would stimulate more at the more tonic end of the loop. As I have considerable evidence to show that the tone of the muscle is actually graded from the duodenum to the ileum (see Chapter VII), we can easily explain the fact that the muscle contracts most actively on the orad side of a bolus.

Keith's Theory. Another question which some have asked is: What is the relation of the gradient theory to the

zone theory of Keith? In two articles published in 1915, Dr. Keith reported the finding of certain cells associated with Auerbach's plexus, cells which he thought were intermediate between muscle and nerve, and which were very similar to those in the Keith-Flack node of the heart. Shortly after making this discovery he read my first two communications on intestinal rhythm, and was much impressed by the fact that the terminal segment of the ileum sometimes sets the pace for a short stretch of bowel immediately above. He argued from that that the little collections of "nodal tissue" which he had found at the cardia and ileocecal sphincter, and other collections which he did not find, but which he thought might be present in the duodenum, upper jejunum and middle small intestine, are centers dominating the rhythm and activity of those sections of the tract. He suggested that the "food is propelled through a series of zones or segments, each furnished with its own pacemaker and its own rhythmical contractions." Intestinal stasis, of the Arbuthnot Lane type, may be due to blocks "at the points where one rhythmical zone or area passes into the succeeding zone." Since then, several writers have been much impressed with this idea. Unfortunately, they seem to have read Dr. Keith's articles only in abstract, because their published diagrams show nodal tissue at the points where Keith says he expected to find it but did not. Moreover, they do not seem to realize that Keith has made no physiological studies at all, but has simply made some suggestions on the basis of his anatomical findings.

The plausible feature about this theory is that we know that in the heart the region with the fastest rate sets the pace for the others. Although to the naked eye the heart seems to contract simultaneously all over, graphic records show that a wave of excitation travels from the sinus to the

ventricles. Somewhat similarly, in the stomach, the area with the most rapid rate at the cardia appears to set the pace and we can see the waves traveling slowly to the pylorus. In the small intestine, however, *each segment contracts at its own rate,* and only occasionally do we see what are called peristaltic rushes running some distance down the bowel. Although the duodenal muscle has the fastest rate it does not set the pace for the rest of the gut. I must emphasize this point because several writers in overlooking it, have theorized unwarrantedly on the basis of Keith's findings. Furthermore, Miss Starkweather and I[18] have made a careful study of the regions suspected by Keith of being pacemakers; we have counted the rates of rhythmic contraction in these segments and in adjoining ones before and after cutting them apart, and we have found no sign of any zones or of any rhythmic domination of one segment over another. Whether the ileocecal ring has much to do with the colonic activities or not I cannot as yet say. We see, then, that although it is often most helpful to make comparisons between the activities of the heart tube and the intestine, they must be made with great care and with due regard for all the facts in the case.

Another objection to arise in the minds of many is: If reverse peristalsis is so common, why do we not see more of it with the roentgen ray? It seems to me that there are several answers to this question. In the first place, it must be remembered that we generally screen patients during intervals when they are not acutely ill and are not showing many symptoms. If we could watch the movements of the bowel in the acute stages of appendicitis, in acute ileus, or during the first two or three days after intra-abdominal operations, we should probably see enough reverse peristalsis. Actually we do see, not infrequently, reverse waves in the

stomach and duodenum. Very rarely I have seen them in the terminal ileum. Unfortunately, the food goes so rapidly through the jejunum and upper ileum that we can seldom see what is going on there.

It must be remembered also that many of the disturbances seem to be due to ripples which are not deep enough to force the barium along the bowel. As I have shown in Chapter IX, there is no doubt that a small peristaltic rush in the lower ileum, or a wave that forces material through the ileocecal sphincter is often part of a ripple that has come from the duodenum. One might not suspect it if it were not shown so clearly on the records obtained with six or seven enterographs, recording simultaneously. These ripples do not move material in the bowel unless they break into peristaltic rushes or into defecating movements in the colon. They are like waves of the ocean which do not carry a boat with them for any distance unless they are breaking on a shelving beach. Similarly, in the digestive tract, ripples in the orad direction breaking into waves at the cardia may cause many of the symptoms of indigestion.

Another point to be remembered is that animal experiments suggest that the gradient may be more nearly flattened or reversed in one segment of the tract than another, so that there may be reverse waves in the stomach and normal ones in the intestine. That would tend to complicate the problem. To my mind, the best answer to be made to those who cannot accept the idea of reverse peristalsis until they see more of it with the roentgen ray is that if they wait for that, they will fail to recognize what is going on in the milder, more common disturbances. Similarly, if they wait to diagnose gall-bladder disease until the patient has colic, jaundice and demonstrable stones, they will miss perhaps 95 per cent of the early cases. It seems reasonable to suppose

that the brain of a sensitive man or child should detect, or in some way become conscious of, abnormalities in peristalsis long before they are severe enough to become visible on the roentgen ray screen. Furthermore, these disturbances are often so transient that it would be hard to demonstrate them objectively.

To illustrate: two healthy boys, seven and eight years of age, respectively, ate heartily of blackberries at dinner. The next morning the younger one had diarrhea, but the elder seemed all right. Early in the afternoon, however, he began to complain of dizziness, a queer feeling of pressure in his pharynx, and recurrent waves of nausea which came every twenty or thirty minutes. Once or twice he retched unsuccessfully. Between the attacks of nausea he played happily. At supper time he made several attempts to eat, but each time said the food would not go down; something seemed to push it back. He then felt like defecating and with the help of an enema passed a hard plug of feces. Shortly afterwards he had a large soft movement containing the remains of the blackberries, and immediately after that he asked for food. He then found he could eat a large meal without any difficulty. This child appears then to have had a series of reverse waves which arose in a colon distended by irritant material. These waves were perceived by him as surges of nausea and dizziness, as a tension in the throat, and an inability to swallow. The upset in the gradient was such that the tract would not accept food. Although these sensations were very definite so far as the child was concerned, it might have been impossible to show much change with the roentgen ray beyond, perhaps, a gastric stasis; and it might have been difficult to show much even with a series of enterographs. If, however, the lower bowel had not been emptied when it was, he probably would have vomited

large amounts of intestinal fluid next day, and a few days later the fluid might have been fecal in character. There would then have been no doubt about the existence of reverse peristalsis.

This case brings up still another point, and that is that we can probably study reversals of peristalsis more satisfactorily in children than in adults. The intestine in children is short, its various parts are functionally knit together, it is very sensitive, and its gradient is easily reversed. Hence it is, perhaps, that organic lesions often produce just those symptoms which would be expected according to the gradient theory. In adults, various complicating factors may enter to obscure the picture.

Another question is: How can signs of reverse peristalsis appear from time to time during digestion, when food is actually going down the tract? This objection does not seem insuperable when we remember that waves can travel at the same time in different directions over one medium. Recently I stood on the banks of a stream which was flowing north. The wind was blowing hard enough to make wavelets traveling in the opposite direction. A passing launch produced other waves which came from the east and were reflected at the shore. Three types of waves could easily be identified going in three directions over water which was flowing in a fourth. It may be that ripples can travel up and down the intestine in much the same way. They may, perhaps, skip regions in which the gradient is fairly normal to produce anastalsis in regions where it is reversed. It must be remembered also that liquids can be forced through portions of the tract in which the gradient is definitely reversed. This is shown by the experiments in which sections of bowel are cut, reversed, and anastomosed again. We know also that fluid introduced into the colon under pressure

can be made to run out at the mouth. Moreover, liquids will go through stretches of bowel in which the muscle is paralyzed or from which it has actually been removed (Kreidl and Müller,[242] Müller and Kondo[335]). We need not think always of the food as going with the gradient and the ripples against it, because in parts of the tract the ripples might conceivably be going with the gradient and the food against it. It must be remembered, of course, that this discussion is at present quite theoretical. There is some analogy, perhaps, in the heart, where the blood may continue to travel in the usual direction, although the electrocardiograph shows that the ventricle is contracting a fraction of a second ahead of the auricle.

The difficulties which have bothered me most have been connected with the lack of absolute parallelism between the various gradients under certain conditions and in some parts of the tract. For instance, although asphyxia and KCN are supposed to affect the metabolic gradient in the same way, and although the tracings shown in figures 17 and 18 are remarkably alike so far as amplitude of contraction is concerned, they are not alike as regards rhythmicity. KCN markedly slows the rate of contraction and asphyxia affects it little or not at all until it is stopped entirely. Moreover, asphyxia has little effect on the colon, while KCN depresses its activities. Theoretically, KCN should have less effect on the colon than on the ileum if the severity of the reaction is dependent solely upon the oxygen need of the tissue.

There are a number of such technical problems which await solution during the coming years, and the answers to them will undoubtedly modify some of my present views. Fortunately, however, the best discoveries often come through the solution of difficulties which at first seem most embarrassing and most disturbing.

Chapter XII

TECHNICAL METHODS AND APPARATUS

As much of the technic for the experiments described in this little book had to be worked out as I went along, and as many details which I learned from Dr. Cannon and others are not to be found in textbooks, it occurred to me that a short chapter on apparatus and methods might be gratefully received, particularly by beginners in this field of research.

As Cannon and Auer have pointed out, the early physiologists were greatly hampered in their study of the intestinal movements by the fact that the opening of the abdomen has a strong inhibiting effect. For this reason most of their conclusions were based on observation of the powerful writhing movements which appear just after the death of an animal. The early studies have little value also because the bowel was allowed to dry in the air; and we know that that has a disturbing effect. In 1871, Sanders and Van Braam Houckgeest made a big improvement by opening the animals under a bath of salt solution. That prevented the drying, but conditions were still not entirely normal. Much work was done with fistulae into various parts of the tract and with balloons passed through the mouth, but here again many objections can be raised.

The Roentgen Ray and the Barium Meal. It was not until 1896, when Professor Bowditch suggested to Cannon, then a student, that he use the newly discovered roentgen ray, that we were supplied with an entirely trust-

worthy method for studying the movements of the alimentary canal (Bowditch[71]). Incidentally, it should be noted that it is this method which is now being used so universally and so satisfactorily in medical practice on man. As this technic for animals is well described on pages 5 to 7 of Cannon's book,[86] I shall not go into details here. Barium sulfate "for *x*-ray use" is now used instead of the bismuth subnitrate which occasionally becomes toxic in the bowel. The best animals to use are tame old female cats which will not object to handling, because any anger or excitement stops the intestinal movements. The most satisfactory apparatus would consist now of a small transformer and a self-rectifying Coolidge tube. If the laboratory budget is low, the student may be able to buy very cheaply an old roentgen ray coil with a mercury jet interrupter. Although these outfits are very satisfactory for radioscopy, dealers in roentgen ray apparatus generally have a roomful of them which they can not sell any more. Great care should be taken to see that the operator is protected from all stray radiations and from contact with the high tension wires. The room must be absolutely dark and after entering it the student should not attempt to work for half an hour or more until his retina is fully adjusted. The roentgen ray method is now little used, probably because there is little hope of seeing anything new which Cannon or the many clinical roentgenologists have not already described. I think, however, that it should be used more and more by the pharmacologists.

Method of Auer. Auer[24] made a number of interesting observations on rabbits whose abdomens were shaved. He found he could watch the movements of the cecum quite satisfactorily through the thin abdominal wall. Very simi-

larly, I have been able to study rhythmic segmentation in people with large hernias, where the bowel lay under a thin coat of peritoneum and skin.

Gastric and Duodenal Tubes. For this technic the reader is referred particularly to the articles by Carlson,[96] and his associates. They have done a lot of excellent physiologic work on the movements of the human stomach, using these tubes and balloons. Most of this work was concerned with the hunger contractions and with secretion. Wheelon and Thomas [444] point out that a balloon which can slip around in the stomach is not likely to give an entirely satisfactory record of what is going on there, so they anchor a special type of metal tambour in the antrum and in the pyloric canal. McClendon[306] (p. 180) has studied the hydrogen ion concentration of the gastric and intestinal juices by letting down a specially designed electrode on the end of a wire.

Fistulae. First should be mentioned the Heidenhain-Pavloff stomach which is so designed that the experimenter can study gastric secretion under many conditions. A flap of stomach wall is dissected up and formed into a pouch which empties externally through a fistula. This technic will be found described in the first chapter of Pavloff's book on "The Work of the Digestive Glands,[355] and in excellent articles in the *Ergebnisse der Physiologie*[354] (1902), and in Tigerstedt's "Handbuch der physiologische Methodik."[356] In order to obtain pure gastric juice, Pavloff performed the operation of esophagotomy on dogs already possessing gastric fistulae; that is, he divided the esophagus in the neck and allowed the upper end to heal into the skin incision. When such dogs are given food it drops out of the esophageal opening, but the psychic stimulus causes a flow of gastric juice.

Thiry studied the intestinal juices by closing off one end of a loop of bowel and sewing the other to an opening in the abdominal wall. Vella[437] brought both ends into the skin incision so as to be able to study the progress of balls and bits of food through the loop. Others have made fistulae into various parts of the intestine in order to study the pyloric function and the succus entericus (Cohnheim and Dreyfus,[117] Best and Cohnheim,[52,53] Baumstark,[37] London,[272] Thomsen,[425] Baumstark and Cohnheim,[38] von Mering,[318] Hirsch[189]). Especially when making duodenal fistulae it is helpful to have the stoma as near as possible to the spine of the animal so that gravity will favor and not hinder the keeping of the animal clean. Another method is to sew the unopened bowel to the skin and then to introduce or remove material with a large hypodermic syringe, the needle of which is thrust through the wall.

Windows. Van Braam Houckgeest[194] tried to use glass windows in the abdominal wall, and others (Sabbatani,[381] Katsch,[226] Katsch and Borchers,[227] and Zondek[456]) have since done considerable work with animals which have been operated upon in this way. Watch glasses or pieces of celluloid are generally used, and with care the animals can be kept alive and well for some time. They are useful for pharmacologic studies or for class demonstrations.

Opening under Salt Solution. For the careful analysis of the intestinal movements it seems to me that we shall have to turn more and more to the method which was devised and first used by Sanders.[382] As his papers were published in a small Dutch journal they dropped into oblivion, and the technic is generally ascribed to Van Braam Houckgeest.[194] Sanders' article shows considerable ability;

and it is interesting that he was the first to describe reverse peristalsis in the colon. Houckgeest's article is also well worth reading to-day. Only with the animal opened can one get the kymographic records which are so essential for the exact analysis of muscular movements and conduction; and only in this way can one orient himself properly so as to know what part of the bowel is being studied; which end orad, etc. The animal can be anesthetized most conveniently with urethan, 2 grams per kilo, by mouth. A catheter can be passed into the esophagus through a hole in a small spindleshaped gag. Every care should be taken to see that this catheter gets into the stomach and not into the trachea. If the animal should show any signs of returning sensation, more urethan should be injected through a fine needle into the duodenum. After the animal is thoroughly anesthetized a canula may be put into the trachea, although this is not always necessary. In order to avoid much of the inhibition which comes from opening the abdomen, the spinal cord should generally be destroyed from a point just above the sacrum to the interscapular region. A small incision is made over the lower lumbar spine; an opening is made between two laminae and a large copper wire is thrust up through the canal as far as the interscapular region. The wound is then closed with a suture. The greatest care should be taken while opening the abdomen to cut exactly in the median line. Only in this way can one avoid hemorrhage which is hard to stop in the bath, and which can soon obscure the field of vision. The animal should be washed and then put into the bath. I use a copper tank, 8 inches wide, 9½ inches deep, and 31 inches long, with an electric heater and thermo-regulator. It has a row of metal eyelets along the bottom, to which the animal's paws may be attached, if necessary. Jacobj[212] used a vertical tank which he thought

had certain advantages. It had a glass window on one side through which the bowel could be observed. The bath should consist either of 0.8% sodium chloride solution or else Locke's solution of the following composition.

NaCl	9.00
KCl	.42
$CaCl_2$ anhydrous	.24
$NaHCO_3$	.20
H_2O	1000.00

I now use the Locke's solution, although I do not know whether the results are any more satisfactory than those with plain salt solution. If good movements are to be obtained, the animal should be fed shortly before anesthetization. Some men give aloin or castor oil the night before, but Taylor and I (Alvarez and Taylor[23]) have shown that purgation alters the gradients and damages the muscle in places. Every care should be taken to get normal and frisky animals. As defecation into the tank is often annoying when working with cats, the rectum can be tied off with a piece of tape. The animal's head can be held in proper position by an ordinary Tschermak head-holder which is fastened to the edge of the tank.

The movements can be observed visually or they can be recorded mechanically by means of balloons or some form of enterograph. The use of balloons is unsatisfactory for several reasons. They are foreign bodies; they block the lumen of the gut; they cause bleeding; and the trauma incident to their introduction often overshadows any other stimuli that one may be trying to record. Of all the methods for recording intestinal contractions mentioned in Tigerstedt's "Handbuch der physiologische Methodik,"[296] the one that comes nearest to the requirements for good work

is the enterograph of Bayliss and Starling. This, however, is rather too elaborate; it is not easily fastened to the bowel wall, and it must be kept above the level of the salt solution.

Figure 22 shows on the left, a type of *enterograph* which I designed several years ago and which has enabled me to get satisfactory records from several parts of the bowel at one

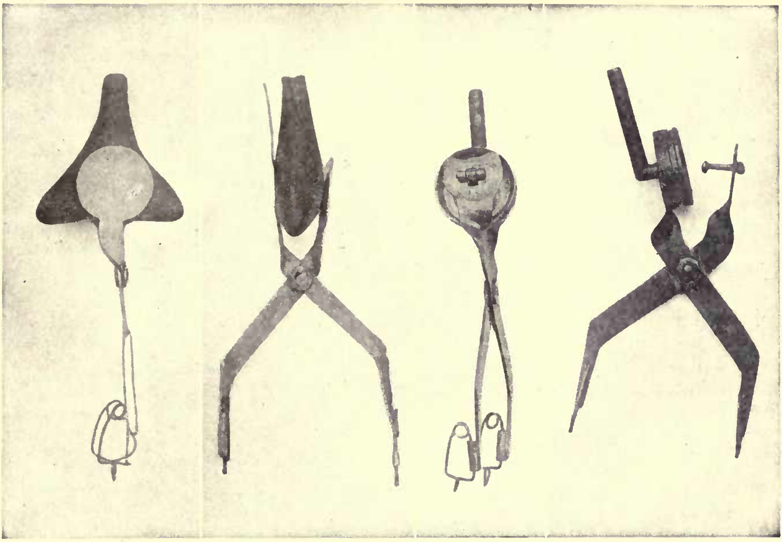

FIG. 22.—On the left is shown the simple type of recorder ordinarily used. On the right is a similar one, made of silver with a small tambour instead of the rubber teat.

time. This simple and cheap little apparatus consists of two pieces of sheet aluminum, two short lengths of piano wire and a small rubber teat. I first used the teat which is made for springing the shutters in large commercial cameras. When the supply of these (from England) was cut off by the war, I used the triangular little bags which are supplied for the ends of stirring rods. The rubber teat should be

cemented to the aluminum only on one side. When fastened on both sides it is likely to bind and the apparatus is less sensitive. The other arm of the little lever is fastened to the peritoneal coat of the bowel by means of a little wire serrefine. This generally has to be made by the student himself if it is to grip firmly and not spring open all the time. A series of these recorders can be fastened to a number of tambours which write one above the other on a smoked surface. For a while, during the war, when I could not get any form of rubber teat I fastened a small tambour to one side of the enterograph as shown in the figure, but I found this less sensitive than the much cheaper and simpler form. The little serrefines are much more convenient than any form of hook or sewed-on apparatus because the tone of the bowel changes rapidly from time to time and the observer must be able to take up slack quickly and without undue handling. The only place where the recorders do not work well is on the colon. That contracts down so hard at times that it tears away from the instruments, leaving them hanging to shreds of peritoneum. When one wishes to record the intestinal movements in only one or two places it is best to follow the technic which I have described elsewhere (Alvarez and Starkweather[18]). One end of a loop is held down by a serrefine fastened on the end of a rod, and the other end pulls on a heart lever which writes on a drum which can be placed over the tank immediately above the animal.

Slowtzoff[402] and Trendelenburg[430] have described methods for recording the contractions of a loop of bowel through holes made through the abdominal wall of an anesthetized animal but I can see no advantages over the tank method if one has a tank handy. Courtade and Guyon[120] used loops of bowel removed from the abdomen but still attached by a section of mesentery. Hofmeister and Schütz[191] did a lot of

work with the excised stomach in a moist chamber. I have found it convenient to run steam from a flask of boiling water into the chamber. It not only keeps the tissue moist, but it keeps it warm. Sick and Tedesco[400] studied the excised stomach in oxygenated Locke's solution. Carnot[99] and Glenard[168] *perfused* the intestine excised from the body as a whole.

Small Excised Segments. Haffter[176] seems to have been the first to learn that excised segments of intestine will continue to contract rhythmically. Magnus[289] deserves most credit for having worked out the details of the method which often goes by his name. I have modified it to the extent that I use several segments at a time in the same bath. The animal is killed with chloroform or with a blow on the head. It is then opened, and pieces from 25 to 50 cm. in length are removed from various parts of the bowel and strung on a safety pin in proper order, and with the orad end towards the pin. These segments can be kept then in iced Locke's solution and smaller pieces cut off as needed during the day. I generally use at least five segments at one time, suspended between serrefines in a beaker containing about 400 c.c. of Locke's solution. This is kept in a water bath at 38° C. It is oxygenated by a small stream of compressed air which bubbles through it. When four or five segments are used at one time they should be cut fairly short; that is, about 2 cm. long, and special levers should be used. The Harvard Apparatus Company (Back Bay postoffice, Boston) made me some, 30 cm. long, with an adjustable pivot so that the ratio between the arms can be varied at will. If the ordinary heart levers are used, the magnification is so great that all the records will not go on a drum of the standard size. If a large amount of Locke's solution is used, the segments con-

tract more regularly and for a longer period of time, probably because their metabolites are well diluted. It is only when using rare drugs or small amounts of vital fluids that one needs to use a smaller amount of solution. As I have pointed out before (Alvarez,[2]) when making pharmacologic studies with such small amounts, one must be careful to see that the temperature remains constant within tenths of a degree; otherwise erroneous conclusions may easily be drawn. Whenever possible, the pharmacologist should use several segments at one time to serve as checks, one on another. Anyone who will look over some of the figures in my sixteenth article (Alvarez[16]) will, I think, be impressed with the need for that precaution.

When studying conduction, the myenteric reflex and other phenomena, the technique described in my eighteenth article (Alvarez and Starkweather[18]) is very useful. There I show how records can be obtained from both ends of a segment by turning them up like a U.

Sometimes it is desired to compare the contractions of the circular and longitudinal muscles, or to study the action of drugs on the inner surface of the bowel. For such work the student may use the technic described by Gayda[162] and Morishima and Fujitani.[326]

For the *latent period work* I have used a simple moist chamber made out of a wide-mouthed six-ounce bottle. The lower end of the segment is fastened by a serre-fine to a metal "L" support which is thrust through the rubber stopper. The other end of the segment is fastened to the metal heart lever by means of a fine copper wire. The current can be led to the segment through these two metal connectons. The apparatus for the metabolic work and the catalase experiments will be found described in articles by Miss Starkweather and me.[11]

The student who plans to do research work in gastro-enterology or the physician who wishes to know more about the mechanical factors of digestion should study carefully Cannon's classic book on the subject. Bayliss and Starling's three articles, and one by Elliott and Barclay-Smith should also be read and re-read. Magnus' articles in the Ergebnisse,[295] and in Tigerstedt's "Handbuch,"[296] are also very helpful. Much good physiology will be found in excellent books and articles by Carman,[98] Barclay,[33] Carlson,[96] Case,[105] and Hurst.[199]

For information on the chemical side of digestion the student should turn to the splendid books of Pavloff,[355] Cohnheim,[116] and Babkin.[27] Babkin is Pavloff's assistant at Petrograd, and his book summarizes the work done in Russia up to the beginning of the War.

Wingate Todd's[427] splendid little book presents the anatomy of the digestive tract from the viewpoint of a man who is thoroughly conversant with the work of the physiologist and the roentgenologist. Those who would like to know something about the comparative anatomy of the tract should turn to Oppel,[346] Huntington,[196] and Mitchell.[322] The subject of comparative physiology has been well covered by Jordan.[222]

The real student of a subject must always know something about its history and development. Access to the older literature can easily be obtained through the little book of Poensgen;[360] and the articles of Cary,[103] Pearce,[357] Cannon,[91] and Crane[121] will be found very interesting. American students will be interested also in the work of Beaumont,[42] the "Backwoods Physiologist." His book contains little of scientific interest for us today, but it makes up for it with the wealth of inspiration which it can give to any young man who, with little outside help or recognition, will struggle onward with his work.

BIBLIOGRAPHY

1. Abel, W. Further observations on the development of the sympathetic nervous system in the chick. *J. Anat. & Physiol.*, 1912, 47, 35–72.

2. Alvarez, W. C. I. Functional variations in contractions of different parts of the small intestine. *Am. J. Physiol.*, 1914, 35, 177–193.

3. Alvarez, W. C. II. Further studies on intestinal rhythm. *Am. J. Physiol.*, 1915, 37, 267–281.

4. Alvarez, W. C. III. The motor functions of the intestine from a new point of view. *J. Am. M. Assn.*, 1915, 65, 388–394.

5. Alvarez, W. C. IV. Differences in rhythmicity and tone in different parts of the wall of the stomach. *Am. J. Physiol.*, 1916, 40, 585–602.

6. Alvarez, W. C. V. Differences in irritability and latent period in different parts of the wall of the stomach. *Am. J. Physiol.*. 1916, 41, 321–332.

7. Alvarez, W. C. VI. Differences in latent period and form of the contraction curve in muscle strips from different parts of the frog's stomach. *Am. J. Physiol.*, 1917, 42, 422–434.

8. Alvarez, W. C. VII. Differences in latent period and form of the contraction curve in muscle strips from different parts of the mammalian stomach. *Am. J. Physiol.* ,1917, 42, 435–449.

9. Alvarez, W. C. IX. The syndrome of mild reverse peristalsis. *J. Am. M. Assn.*, 1917, 69, 2018–2024.

10. Alvarez, W. C. X. Differences in the behavior of segments from different parts of the intestine. *Am. J. Physiol.*, 1918, 45, 342–350.

11. Alvarez, W. C. and Starkweather, E. XI. The metabolic gradient underlying intestinal peristalsis. *Am. J. Physiol.*, 1918, 46, 186–208.

12. Alvarez, W. C. XII. The influence of drugs on intestinal rhythmicity. *Am. J. Physiol.*, 1918, 46, 554–562.

13. Alvarez, W. C. and Starkweather, E. XIII. The motor functions of the cecum *Am. J. Physiol.*, 1918, 46, 563–569.

14. Alvarez, W. C. and Starkweather, E. XIV. Differences in the catalase content of muscle from different parts of the stomach. *Am. J. Physiol.*, 1918, 47, 60–66.

15. Alvarez, W. C. and Starkweather, E. XV. The catalase content of the mucous membrane from different parts of the digestive tract. *Am. J. Physiol.*, 1918, 47, 67–75.

16. Alvarez, W. C. XVI. Differences in the action of drugs on different parts of the bowel. *J. Pharmacol. & Exper. Therap.*, 1918, 12, 171–191.

17. ALVAREZ, W. C. and STARKWEATHER, E. XVII. The metabolic gradient underlying colonic peristalsis. *Am. J. Physiol.*, 1918, 47, 293–301.

18. ALVAREZ, W. C. and STARKWEATHER, E. XVIII. Conduction in the small intestine. *Am. J. Physiol.*, 1919, 50, 252–265.

19. ALVAREZ, W. C. The origin of the so-called autointoxication symptoms. *J. Am. M. Assn.*, 1919, 72, 8–13.

20. ALVAREZ, W. C. The metabolic gradient underlying peristalsis. *J. Am. M. Assn.*, 1919, 73, 1438–1440.

21. ALVAREZ, W. C. XX. Recent advances in gastric physiology. *Am. J. M. Sci.*, 1919, 158, 609–619.

22. ALVAREZ, W. C. XXI. Peristalsis in health and disease. *Am. J. Roentg.*, 1921, 8, 1–11.

23. ALVAREZ, W. C. and TAYLOR, F. B. Changes in rhythmicity, irritability and tone in the purged intestine. *J. Pharmcol. & Exper. Therap.*, 1917, 10, 365–377.

24. AUER, J. Gastric peristalsis in rabbits under normal and some experimental conditions. *Am. J. Physiol.*, 1907, 18, 347–361.

25. AUFSCHNAITER, O. V. Die Muskelhaut des menschlichen Magens. *Wien. Sitzungsb. d.k. Akad. d. Wissensch.*, 1894, 103, abth. 3, 75–96.

26. AUSTIN, A. E. Diseases of the digestive tract and their treatment. St. Louis, 1916.

27. BABKIN, B. P. Die äussere Sekretion der Verdauungsdrüsen. Berlin, 1914.

28. BABKIN, B. P. The influence of natural chemical stimuli on the movements of the small intestine. *Physiolog. Abstracts*, 1917, 2, 42–43.

29. BANCROFT, F. W. and ESTERLY, C. O. A case of physiological polarization of the ascidian heart. *Univ. Calif. Pub. Zool.*, 1903, 1, 105–114.

30. BARBERA, A. G. Über die Reizbarkeit des Froshmagens. *Ztschr. f. Biol.*, 1898, 36, 239–258.

31. BARCLAY, A. E. The normal and pathological stomach as seen by the x-rays. *Brit. M. J*, 1910, 2, 537–541.

32. BARCLAY, A. E. Note on the movements of the large intestine. *Arch. Roentg. Ray*, 1912, 16, 422–424.

33. BARCLAY, A. E. The stomach and esophagus. London, 1913.

34. BARCLAY, A. E. The etiology of gastric ulcer. *Arch. Roentg. Ray.*, 1913, 18, 234–238.

35. BARCLAY, A. E. Radiological studies of the large intestine. *Brit. J. Surg.*, 1915, 2, 638–652.

36. BARRATT, W. On the anatomical structure of the vagus nerve. *J. Anat. & Physiol.*, 1898, 32, 422–427.

37. BAUMSTARK, R. Über Hervorrufung von Magenfunktions-störungen vom Darm aus. *Ztschr. f. phys. Chemie*, 1913, 84, 437–450.

38. BAUMSTARK, R. and COHNHEIM, O. Zur Physiologie der Darmbewegungen und der Darmverdauung. *Ztschr. f. phys. Chemie*, 1910, 65, 483–488.

39. BAYLISS, W. M. and STARLING, E. H. The movements and innervation of the small intestine. *J. Physiol.*, 1899, 24, 99–143.

40. BAYLISS, W. M. and STARLING, E. H. The movements and innervation of the large intestine. *J. Physiol.*, 1900, 26, 107–118.

41. BAYLISS, W. M. and STARLING, E. H. The movements and innervation of the small intestine. *J. Physiol.*, 1901, 26, 125–138.

42. BEAUMONT, W. Experiments and observations on the gastric juice and the physiology of digestion. Plattsburgh, 1833.

43. BECHTEREW, W. von and WEINBERG. Die Functionen der Nervencentra. Jena, 1908, I, p. 259.

44. BEER, E. and EGGERS, C. Are the intestines able to propel their contents in an antiperistaltic direction? *Ann. Surg.*, 1907, 46, 576–588.

45. BEITZKE. Zur Histologie der chronischen Gastritis. *Verhandl. d. deutsch. path. Gesellsch.*, 1914, 17, 433–435.

46. BELLAMY, A. W. Differential susceptibility as a basis for modification and control of early development in the frog. *Biol. Bull.*, 1919, 37, 312–361.

47. BENSLEY, R. R. The cardiac glands of mammals. *Am. J. Anat.*, 1902, 2, 105–156.

48. BERCOVITZ, Z. and Rogers, F. T. The inhibitory effects of vagus stimulation on gastric motility in the turtle. *Am. J. Physiol.*, 1921, 55, 310.

49. BERGMANN, G. von. Zur diagnostischen Bedeutung der Pylorusfunction. *Zentralbl. f. Roentgenstr.*, 1913, 4, 1–5.

50. BERNHEIM, A. Movements of the intestines. *J. Am. M. Assn.*, 1901, 36, 429–431.

51. BEST, F. and COHNHEIM, O. Über den Rückfluss von Galle in den Magen bei Fettfütterung. *Ztschr. f. phys. Chemie*, 1910, 69, 125–126.

52. BEST, F. and COHNHEIM, O. Über Bewegungsreflexe des Magendarmkanals. *Ztschr. f. phys. Chemie*, 1910, 69, 113–116.

53. BEST, F. and COHNHEIM, O. Zur Röntgenuntersuchung des Verdauungskanals. *München. Med. Wchnschr.*, 1911, 58, 2732–2734.

54. BETHE, A. Das Centralnervensystem von Carcinus Maenas. *Arch. f. mikr. Anat. u. Entwickgesch.*, 1898, 51, 382–452.

55. BETHE, A. Allgemeine Anatomie und Physiologie des Nervensystems, p. 100. Leipzig, 1903.

56. BIEDERMANN, W. Zur Physiologie der glatten Muskeln. *Arch. f. d. ges. Physiol.*, 1889, 45, 369–388.

57. BIEDERMANN, W. Studien zur vergleichenden Physiologie der peristaltischen Bewegungen. I. Die peristaltischen Bewegungen der Würmer und Tonus der glatter Muskeln. *Arch. f. d. ges. Physiol.*, 1904, 102, 475–541.

58. BIEDERMANN, W. Studien zur vergleichenden Physiologie der peristaltischen Bewegungen. II. Die locomotorischen Wellen der Schneckensohle. *Arch. f. d. ges. Physiol.*, 1905, 107, 1–56.

59. BIEDERMANN, W. Studien zur vergleichenden Physiologie der peristaltischen Bewegungen. III. Die Innervation der Schneckensohle. *Arch. f. d. ges. Physiol.*, 1906, **111**, 251–297.

60. BINE, R. and SCHMOLL, E. The treatment of gastric and duodenal ulcer. *Calif. State J. M.*, 1914, **12**, 361–366.

61. BOKAI, A. Experimentelle Beiträge zur Kenntniss der Darmbewegungen. *Arch. f. exper. Path. u. Pharmakol.*, 1887, **24**, 153–166.

62. BOLDIREFF, W. Über den Übergang der natürlichen Mischung des Pankreas, des Darmsaftes und der Galle in den Magen. Die Bedingungen und wahrscheinliche Bedeutung dieser Erscheinung. *Zentralbl. f. Physiol.*, 1904, **18**, 457–460.

63. BOLDIREFF, W. Die periodische Tätigkeit des Verdauungsapparates ausser der Verdauungszeit. *Zentralbl. f. Physiol.*, 1904, **18**, 489–493.

64. BORGBJÄRG, A. Verzögerung der Magenentleerung bei Darmkrankheiten. *Archiv. f. Verdauungskr.*, 1911, **17**, 706–721.

65. BORING, E. G. The sensations of the alimentary canal. *Am. J. Psychol.*, 1915, **26**, 1–57.

66. BOSE, J. C. Researches on the irritability of plants. London, 1913.

67. BOTTAZZI, F. Contributions to the physiology of unstriated muscular tissue. Part IV. The action of electrical stimuli upon the oesophagus of Aplysia Depilans and Aplysia Limacina. *J. Physiol.*, 1898, **22**, 481–506.

68. BOTTAZZI, F. Untersuchungen über das viscerale Nervensystem der decapoden Crustacean. *Ztschr. f. Biol.*, 1902, **43**, 341–371.

69. BOTTAZZI, F. Untersuchungen über das viscerale Nervensystem der Selachier. *Ztschr. f. Biol.*, 1902, **43**, 372–442.

70. BOTTAZZI, F. and GRÜNBAUM, O. F. F. On plain muscle. *J. Physiol.*, 1899, **24**, 51–71.

71. BOWDITCH, H. P. *Science*, 1897, **5**, 901–902.

72. BRANDL, J. and TAPPEINER, H. Versuche über Peristaltik nach Abführmitteln. *Arch. f. exper. Path. u. Pharmakol.*, 1889, **26**, 177–185.

73. BRINTON, W. The diseases of the stomach. London, 1859.

74. BRÜCKE, E. von. Zur Physiologie der Kropfmusculatur von Aplysia Depilans. *Arch. f. d. ges. Physiol.*, 1905, **108**, 192–215.

75. BRÜCKE, E. von. Versuche an ausgeschnittenen und nach einer Drehung um 180° reimplantierten Flimmerschleimhaut Stücken. *Arch. f. d. ges. Physiol.* 1916, **166**, 45–54.

76. BUCHANAN, F. Dissociation of auricles and ventricles in hibernating dormice. *J. Physiol.*, 1911, **42**, xix–xx.

77. BUNCH, J. L. On the origin, course and cell-connections of the visceromotor nerves of the small intestine. *J. Physiol.*, 1898, **22**, 357–379.

78. BURROWS, M. T. Rhythmical activity of isolated heart muscle cells in vitro. *Science*, 1912, **36**, 90–92.

79. CAMPBELL, H. F. Rectal alimentation in the nausea and inanition of

pregnancy. Intestinal inhaustion, an important factor and the true solution of its efficiency. *Tr. Am. Gynec. Soc.*, 1878, 3, 268–298.

80. CANNON, W. B. The movements of the intestines studied by means of the roentgen rays. *Am. J. Physiol.*, 1902, 6, 251–277.

81. CANNON, W. B. The motor activities of the stomach and small intestine after splanchnic and vagus section. *Am. J. Physiol.*, 1906, 17, 429–442.

82. CANNON, W. B. Recent advances in the physiology of the digestive organs bearing on medicine and surgery. *Am. J. M. Sc.*, 1906, 131, 563–578.

83. CANNON, W. B. The acid control of the pylorus. *Am. J. Physiol.*, 1907, 20, 283–322.

84. CANNON, W. B. Further observations on the myenteric reflex. *Am. J. Physiol.*, 1908, 23, xxvi–xxvii.

85. CANNON, W. B. The influence of emotional states on the functions of the alimentary canal. *Am. J. M. Sc.*, 1909, 137, 480–487.

86. CANNON, W. B. The mechanical factors of digestion. New York, 1911.

87. CANNON, W. B. The importance of tonus for the movements of the alimentary canal. *Arch. Int. Med.*, 1911, 8, 417–426.

88. CANNON, W. B. The relation of tonus to antiperistalsis in the colon. *Am. J. Physiol.*, 1911, 29, 238–249.

89. CANNON, W. B. The nature of gastric peristalsis. *Am. J. Physiol.*, 1911, 29, 250–266.

90. CANNON, W. B. Peristalsis, segmentation, and the myenteric reflex. *Am. J. Physiol.*, 1912, 30, 114–128.

91. CANNON, W. B. Early use of the roentgen ray in the study of the alimentary canal. *J. Am. M. Assn.*, 1914, 62, 1–3.

92. CANNON, W. B. and BLAKE, J. B. Gastro-enterostomy and pyloroplasty. *Ann. Surg.*, 1905, 41, 686–711.

93. CANNON, W. B. and MURPHY, F. T. The movements of the stomach and intestines in some surgical conditions. *Ann. Surg.*, 1906, 43, 512–536.

94. CARLSON, A. J. Physiology of the ventral nerve cord of myriapoda. *J. Exper. Zool.*, 1904, 1, 269–287.

95. CARLSON, A. J. V. The influence of stimulation of the gastric mucosa on the contractions of the empty stomach (hunger contractions) in man. *Am. J. Physiol.*, 1913, 32, 245–263.

96. CARLSON, A. J. The control of hunger in health and disease. Chicago, 1916.

97. CARLSON, A. J. and BRAAFLADT, L. H. Contributions to the physiology of the stomach. XVIII. On the sensibility of the gastric mucosa. *Am. J. Physiol.*, 1915, 36, 153–170.

98. CARMAN, R. D. The roentgen diagnosis of diseases of the alimentary canal. 2d ed. Philadelphia, 1920.

99. CARNOT, P. Les mouvements de l'estomac et du duodenum étudies par la méthode de la perfusion. *Compt. rend. Soc. de Biol.*, 1913, 74, 1265–1268.

100. Carnot, P. and Glenard, R. Sur la technique de la perfusion intestinale. Facteurs mecaniques influencant la vitesse de la perfusion intestinale. *Compt. rend. Soc. de Biol.*, 1912, **72**, 496–499, 661–664.

101. Carnot, P. and Glenard, R. De la perfusion intestinale chez l'animal vivant. *Compt. rend. Soc. de Biol.*, 1913, **74**, 328–331.

102. Carpenter, F. W. and Conel, J. L. A study of ganglion cells in the sympathetic nervous system, with special reference to intrinsic sensory neurons. *J. Comp. Neurol.*, 1914, **24**, 269–281.

103. Cary, R. J. Digestion: A historical survey. *Johns Hopkins Hosp. Bull.*, 1916, **27**, 142–152.

104. Case, J. T. A critical study of intestinal stasis with new observations respecting the causes of ileal stasis. *Arch. Roentg. Ray*, 1914, **19**, 45–52.

105. Case, J. T. X-ray observations on colonic peristalsis and antiperistalsis with special reference to the function of the ileocolic valve. *Proc. 17th Internat. Congr. Med.*, 1914, Sec. 22, Radiology, Pt. 2, 11–41.

106. Case, J. T. The *x*-ray investigation of the colon. *Arch. Roentg. Ray*, 1915, **19**, 375–387.

107. Case, J. T. Basic considerations in the roentgen study of intestinal stasis. *Penn. M. J.*, 1915, **18**, 683–704.

108. Cash, J. T. Intestinal rest and movement. *Proc. Roy. Soc. Lond.*, 1886, **41**, 212.

109. Chase, M. R. An experimental study of the vagus nerve. *J. Comp. Neurol.*, 1916, **26**, 421–428.

110. Child, C. M. Studies on the dynamics of morphogenesis and inheritance in experimental reproduction. VII. The stimulation of pieces by section in planaria dorotocephala. *J. Exper. Zoöl.*, 1914, **16**, 413–441.

111. Child, C. M. Senescence and Rejuvenescence. Chicago, 1915.

112. Child, C. M. The gradient in susceptibility to cyanides in the meridional conducting path of the ctenophore mnemiopsis. *Am. J. Physiol.*, 1917, **43**, 87–112.

113. Child, C. M. Some considerations concerning the nature and origin of physiological gradients. *Biol. Bull.*, 1920, **39**, 147–187.

114. Chlumskij, Über die Gastroenterostomie. *Beitr. z. klin. Chir.*, 1898, **20**, 487–544.

115. Cohn, M. Röntgenuntersuchung einer Frau, welcher der Magen und beide Nervi vagi reseziert worden sind. *Berl. klin. Wchnschr.*, 1913, **50**, 1393–1395.

116. Cohnheim, O. Die Physiologie der Verdauung und Ernährung. Berlin, 1908.

117. Cohnheim, O. and Dreyfus, G. L. Zur Physiologie und Pathologie der Magenverdauung. *München Med. Wchnschr.*, 1908, **55**, 2484–2485.

118. Cohnheim, O. and Dreyfus, G. L. Zur Physiologie und Pathologie der Magenverdauung. *Ztschr. f. phys. Chemie*, 1908, **58**, 50–83.

119. COLE, L. G. Relation of lesions of the small intestine to disorders of the stomach and cap as observed roentgenologically. *Am. J. M. Sc.*, 1914, **148**, 92–118.

120. COURTADE, D. et GUYON, J. F. Influence motrice du grand sympathique sur l'intestin grêle. *Arch. d. Physiol.*, 1897, **9**, 422–433.

121. CRANE, A. W. American priority in the use of bismuth for the examination of the human stomach. *Am. J. Roentgenol.*, 1915, **2**, 692–696.

122. CULLIS, W. and TRIBE, E. M. Distribution of nerves in the heart. *J. Physiol.*, 1913, **46**, 141–150.

123. CUNNINGHAM, D. J. The varying form of the stomach in man and the anthropoid apes. *Tr. Roy. Soc. Edinb.*, 1906, **45**, 9–47.

124. DEAVER, J. B. Appendicitis. Philadelphia, 1905.

125. DEMARQUAY. Recherches faites sur un malade affecte d'anus contre nature. *Union méd.*, 1874, **18**, 906–911.

126. DAGAEW, W. F. Aenderungen in den Verdauungsprozessen nach Gastroduodenostomie und Gastrojejunostomie und nach totaler Magenexstirpation. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1913, **26**, 176–194.

127. DIETERLEN, F. Über das Aufwärtswandern der Bakterien im Verdauungskanal und seine Bedeutung für die Infektion des Respiratsionstraktus. *Zentralbl. f. Bakteriol.*, Part 1, Orig., 1907, **45**, 385–387.

128. DIETLEN, H. Die Insuffizienz der Valvula ileocoecalis im Röntgenbild. *Fortschr. a. d. Geb. d. Röntgenstr.*, 1914, **21**, 23–30.

129. DITTLER, R. Über den Erregungsablauf am Kropfe der Aplysia. *Arch. f. d. ges. Physiol.*, 1911, **141**, 527–540.

130. DRUMMOND, H. Observations on the functions of the colon, with special reference to the movements of enemata. *Brit. M. J.*, 1914, **1**, 240–242.

131. DUCCESCHI, V. Gastric studies. *Arch. per le sc. med.*, 1897, **21**, 134–137.

132. EDGEWORTH, F. H. On a large fibred sensory supply of the thoracic and abdominal viscera. *J. Physiol.*, 1892, **13**, 260–271.

133. EDMUNDS, C. W. The point of attack of certain drugs acting on the periphery. II. Action on the retractor penis of the dog. *J. Pharmacol. & Exper. Therap.*, 1920, **15**, 201–216.

134. EGAN, E. Azidität und Entleerung. Untersucht mittelst Dauermagensonde und Durchleuchtung. *Arch. f. Verdauungskr.*, 1915, **21**, 479–496.

135. EGGLESTON, C. and HATCHER, R. A. The seat of the emetic action of various drugs. *J. Pharmacol. & Exper. Therap.*, 1915, **7**, 225–253.

136. ELLIOTT, T. R. On the innervation of the ileocolic sphincter. *J. Physiol.*, 1904, **31**, 157–168.

137. ELLIOTT, T. R. The action of adrenalin. *J. Physiol.*, 1905, **32**, 401–467.

138. ELLIOTT, T. R. and BARCLAY-SMITH, E. Antiperistalsis and other muscular activities of the colon. *J. Physiol.*, 1904. **31**, 272–304.

139. ENDERLEN and HESS. Über Antiperistaltik. *Deutsche Ztschr. f. Chir.*, 1901, **59**, 240–253.

140. Engelmann, T. W. Zur Physiologie des Ureter. *Arch. f. d. ges Physiol.*, 1869, 2, 243–293.

141. Engelmann, T. W. and von Brakel, G. IV. Über die peristaltische Bewegung, insbesondere des Darms. *Arch. f. Physiol.*, 1871, 4, 33–50.

142. Eppinger, H. and Hess, L. Vagotonia: A clinical study in vegetative neurology. Translation by Kraus and Jelliffe, 2nd rev. ed. New York, 1917.

143. Esslemont, J. E. Beiträge zur pharmakologischen Wirkung von Abführmittel der Aloëderivatgruppe. *Arch. f. exper. Path. u. Pharmakol.*, 1900, 43, 274–285.

144. Ewald, C. A. Über ein wenig beachtetes Frühsymptom des Ileus. *Berl. klin. Wchnschr.*, 1907, 44, 1416–1417.

145. Exner, A. Wie schützt sich der Verdauungstract vor Verletzungen durch spitze Fremdkörper? *Arch. f. d. ges. Physiol.*, 1902, 89, 253–280.

146. Eyster, J. A. E. and Meek, W. J. Experiments on the origin and propagation of the impulse in the heart. *Heart*, 1914, 5, 119–134.

147. Farr, R. E. Abdominal surgery under local anesthesia. *J. Am. M. Assn.*, 1919, 73, 391–395.

148. Faulhaber, M. and von Redwitz, E. F. Über den Einfluss der "circulären Magenresektion" auf die Sekretion und Motilität des Magens. med. klin., 1914, 10, 680–684.

149. Faulhaber, M. and von Redwitz, E. F. Zur Klinik und Behandlung des "pylorusfernen" Ulcus ventriculi. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1915, 28, 150–212.

150. Fisher, H. G. Histological structure of the retractor penis muscle of the dog. *Anat. Record*, 1917, 13, 69–79.

151. Fletcher, W. M. Preliminary note on the motor and inhibitor nerve-endings in smooth muscle. *J. Physiol.*, 1898, 22, xxxvii–xl.

152. Flint, A. A text book of human physiology. New York, 1895, 4th ed.

153. Flöel, O. Die Wirkung der Kalium- und Natrium-Salze auf die glatte Muskulatur verschiedener Thiere. *Arch. f. d. ges. Physiol.*, 1885, 35, 157–173.

154. Forbes, A. and Gregg, A. II. The correlation between strength of stimuli and the direct and reflex nerve response. *Am. J. Physiol.*, 1915, 39, 172–235.

155. Friedländer, B. Über das Kriechen der Regenwürmer. *Biol. Centralbl.* 1888, 8, 363–366.

156. Fubini, S. Einfluss der Elektrischen Inductionsströme, des Kochsalzes und der Tinctura opii crocata auf die Geschwindigkeit der Bewegungen des Dünndarms. *Centralbl. f. d. med. Wissensch.*, 1882, 26, 579–581.

157. Garrey, W. E. The temperature coefficient of the neurogenic rhythm of the heart of Limulus Polyphenus. *J. Physiol.*, 1920, 3, 41–48.

158. Gaskell, W. H. On the innervation of the heart, with especial reference to the heart of the tortoise. *J. Physiol.*, 1883, 4, 43–127.

159. Gaskell, W. H. The contraction of cardiac muscle. Schaefer's Text-book of Physiology, Edinburgh and London, 1900, 2, 169–227.

160. Gaskell, W. H. The involuntary nervous system. London, 1916.

161. Gault, C. C. The physiology of the atrio-ventricular connection in the turtle. III. The influence of the vagi and of the sympathetic nerves on its rhythm-forming power. *Am. J. Physiol.*, 1917, **43**, 22–42.

162. Gayda, T. Beiträge zur Physiologie das überlebenden Dünndarms von Säugetieren. *Arch. f. d. ges. Physiol.*, 1913, **151**, 407–455.

163. Gehuchten, A. von. Recherches histologiques sur l' appareil digestif de la larve de la Ptychoptera Contaminata. *La Cellule*, 1890, **6**, 183–292.

164. Gerlach, L. Über den Auerbachschen Plexus myentericus. *Ber. ü. d. Verhandl. d. k. sächs. Gesellsch. d. Wissensch.*, Leipz., math.-phys. Klasse, 1873, **25**, 1–10.

165. Gilmer. Effects of good or bad taste of the contrast meal—Abstract. *Zentralbl. f. Röntgenstr.*, 1911, 2, 235.

166. Ginsburg, H., Tumpowsky, I. and Hamburger, W. W. Contributions to the physiology of the stomach. XXXV. The newer interpretation of the gastric pain in chronic ulcer. *J. Am. M. Assn.*, 1916, **67**, 990–994.

167. Glaister, J. and Logan, D. D. Gas poisoning in mining and other industries. Edinburgh, 1914.

168. Glenard, R. Les mouvements delintestin en circulation artificielle. *Arch. de. mal. de l'appar. digest.*, 1915, 8, 61–95.

169. Greene, C. W. and Gilbert, N. C. II. The electrocardiogram during extreme oxygen-want. *Am. J. Physiol.*, 1920, **51**, 181.

170. Groedel, F. M. Die Magenbewegungen. Hamburg, 1912.

171. Grützner, P. Die glatten Muskeln. *Ergebn. d. Physiol.*, 1904, 3, part 2, 12–88.

172. Grützner, P. Zur Physiologie der Darmbewegung. *Deutsche med. Wchnschr.*, 1894, 20, 897–898.

173. Grützner, P. Über die Bewegungen des Darminhaltes. *Arch. f. d. ges. Physiol.*, 1898, **71**, 492–522.

174. Gunn, J. A. and Underhill, S. W. F. Experiments on the surviving mammalian intestine. *Quart. J. Physiol.*, 1914, 8, 275–296.

175. Haane, G. Über die Cardiadrüsen und die Cardiadrüsenzone des Magens der Haussäugethiere. *Arch. f. Anat. u. Physiol.*, 1905, Anat. Abth., 1–32.

176. Haffter, W. Neue Versuche über den Nervus splanchnicus major. Henle u. Pfeufer, *Ztschr. f. rat. Med.*, 1854, 4, 322–329.

177. Hall, M. Diaperistaltic and antiperistaltic action. *Lancet*, 1857, **1**, 82–83.

178. Halsey, J. T. The digitalized dog's heart as affected by amyl nitrite or atropine, studied electrocardiographically. *J. Exper. M.*, 1917, 25, 729–754.

179. Hart, T. S. Paroxysmal tachycardia. *Heart*, 1912, 4, 128–136.

180. HAUDEK, M. and STIGLER, R. Radiologische Untersuchungen über den Zusammenhang zwischen Austreibungszeit des normalen Magens und Hungergefühl. *Arch. f. d. ges. Physiol.*, 1910, **133**, 145–160.

181. HECHT, S. The physiology of the blood system of Ascidia Atra Lenseur. *Am. J. Physiol.*, 1918, **45**, 157–187.

182. HEDBLOM, C. A. and CANNON, W. B. Some conditions affecting the discharge of food from the stomach. *Am. J. M. Sc.* 1909, **108**, 504–521.

183. HEILE, B. Experimentelle Beobachtungen über die Resorption im Dünn-und Dickdarm. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1905, **14**, 474–486.

184. HEMMETER, J. C. Beiträge zur Antiperistaltik des Darms. *Arch. f. Verdauungskr.*, 1902, **8**, 59–74.

185. HERMANN, L. Neue Untersuchungen über Hautströme. *Arch. f. d. ges. Physiol.*, 1882, **27**, 280–288.

186. HERSCHELL, G. Gastric trouble of urinary origin. *Med. Press Circ.*, 1905, **130**, 559–560.

187. HESS, J. Versuche über die peristaltische Bewegung und über die Wirkung der Abführmittel. *Deutsches Arch. f. klin. Med.*, 1886, **40**, 93–116.

188. HIPPOCRATES, The works of. Adam's Translation, New York, vol. II, 252.

189. HIRSCH, A. Weitere Beiträge zur motorischen Funktion des Magens nach Versuchen an Hunden mit Darmfisteln. *Zentralbl. f. klin. Med.*, 1893, 377–383.

190. HIRSCH, E. F. The gastric mucosa in delirium tremens. *Arch. Int. Med.*, 1916, **17**, 354–362.

191. HOFMEISTER, F. and SCHÜTZ, E. Über die automatischen Bewegungen des Magens. *Arch. f. exper. Path. u. Pharmakol.*, 1885, **20**, 1–33.

192. HOLZKNECHT, G. Die normale Peristaltik des Kolon. *München. med. Wchnschr.*, 1909, **56**, 2401–2403.

193. HOOKER, D. H. The effect of reversal of a portion of the spinal cord at the stage of the closed neural folds on the healing of the cord wounds, on the polarity of the elements of the cord and on the behavior of frog embryos. *J. Comp. Neurol.*, 1917, **27**, 421–449.

194. HOUCKGEEST, Van Braam. Untersuchungen über Peristaltik des Magens und Darmkanals. *Arch. f. d. ges. Physiol.*, 1872, **6**, 266–302.

195. HUNTER, G. W. JR. Notes on the heart action of Molgula Manhattensis (Verrill). *Am. J. Physiol.*, 1903, **10**, 1–27.

196. HUNTINGTON, G. S. The anatomy of the human peritoneum and abdominal cavity. Philadelphia, 1903.

197. HURST, A. F. The passage of food along the human alimentary canal. *Guy's Hosp. Rep.*, 1907, **61**, 389–427.

198. HURST, A. F. The study of constipation by means of the *x*-rays. *Arch. Roentg. Ray*, 1908, **13**, 3–10.

199. HURST, A. F. Constipation and allied disorders. London, 1909.

200. HURST, A. F. Diagnosis and treatment of duodenal ulcer. *Proc. Roy. Soc. Med.*, 1910, 3, Surg. Sect., 100–107.

201. HURST, A. F. The sensibility of the alimentary canal. London, 1911.

202. HURST, A. F. Common fallacies in the *x*-ray diagnosis of disorders of the alimentary canal. *Arch. Roentg. Ray.*, 1912, 17, 216–219.

203. HURST. A. F. The ileo-caecal sphincter. *J. Physiol.*, 1913, 47, 54–56.

204. HURST, A. F. The cause and treatment of certain unfavorable after-effects of gastroenterostomy. *Ann. Surg.*, 1913, 58, 466–472.

205. HURST, A. F. and NEWTON, A. The normal movements of the colon in man. *J. Physiol.*, 1913, 47, 57–65.

206. HUTCHISON, R. Conditions which simulate dyspepsia. *Brit. M. J.*, 1910, 1, 485–488.

207. HYMAN, L. H. Physiological studies on planaria. I. Oxygen consumption in relation to feeding and starvation. *Am. J. Physiol.*, 1919, 49, 377–402.

208. HYMAN, L. H. On the action of certain substances on oxygen consumption. Action of potassium cyanide on planaria. *Am. J. Physiol.*, 1919, 48, 340–371.

209. HYMAN, L. H. Physiological studies on planaria. II. Oxygen consumption in relation to regeneration. *Am. J. Physiol.*, 1919, 50, 67–81.

210. HYMAN, L. H. Physiological studies on planaria. III. Oxygen consumption in relation to age (size)differences. *Biol. Bull.*, 1919, 37, 388–403.

211. INGVAR, S. Reaction of cells to the galvanic current in tissue cultures. *Proc. Soc. Exper. Biol. & Med.*, 1920, 17, 198.

212. JACOBJ, C. Pharmakologische Untersuchung über das Colchicumgifte. *Arch. f. exper. Path. u. Pharmakol.*, 1890, 27, 119–157.

213. JACOBJ, C. Beiträge zur physiologischen und pharmakologischen Kenntniss der Darmbewegungen mit besonderer Berücksichtigung der Beziehung der Nebenniere zu denselben. *Arch. f. Exper. Path. u. Pharmakol.*, 1891, 29, 171–211.

214. JEFFERSON, G. The human stomach and the canalis gastricus. *J. Anat. & Physiol.*, 1915, 49, 165–181.

215. JENKINS, O. P. and CARLSON, A. J. The rate of nervous impulse in certain molluscs. *Am. J. Physiol.*, 1903, 8, 251–268.

216. JENNINGS, H. S. Modifiability in behavior. I. Behavior of sea anemones. *J. Exper. Zoöl.*, 1905, 2, 447–472.

217. JOHNSON, S. E. On the question of commissural neurones in the sympathetic ganglia. *J. Comp. Neurol.*, 1918, 29, 385–404.

218. JONAS, S. Über das Verhältniss zwischen Stuhlbild und Darmmotilität und die wechselnden Stuhlbilder der Hyperacidität und der Achylie. *Arch. f. Verdauungskr.*, 1912, 18, 769–784.

219. JONNESCO, T. Structure de l'intestin grêle. Poirier et Charpy, Traité d'Anatomie Humaine, 2d ed., Paris, 1901, p. 284.

220. JORDAN, H. Die Physiologie der Locomotion bei Aplysia limacina. *Ztschr. f. Biol.*, 1901, 41, 196–238.

221. JORDAN, H. Über reflexarme Tiere. *Ztschr. f. allg. Physiol.*, 1908, 7, 86–135.

222. JORDAN, H. Vergleichende Physiologie wirbelloser Tiere. Jena, 1913.

223. KÄSTLE und BRUEGEL. Die Bewegungsvorgänge des menschlichen Dünn- und Dickdarmes während der Verdauung auf Grund röntgenographischer und röntgenkinematographischer Untersuchungen. *München. med. Wchnschr.*, 1912, 59, 446–448.

224. KAST, L. Rückläufige Strömung in der Speiseröhre als Erklärung der belegten Zunge. *Berl. klin. Wchnschr.*, 1906, 43, 947–950.

225. KANTOR, J. A study of atmospheric air in the upper digestive tract. *Am. J. M. Sc.*, 1918, 155, 829–857.

226. KATSCH, G. Beiträge zum Studium der Darmbewegungen. III Mitteilung. Pharmakologische Einflüsse auf den Darm bei physiologischer Versuchsanordnung. *Ztschr. f. exper. Path. u. Therap.*, 1913, 12, 253–289.

227. KATSCH, G. and BORCHERS, E. Beiträge zum Studium der Darmbewegungen. I Mitteilung. Das Experimentelle Bauchfenster. *Zeitschr. f. exper. Path. u. Therap.*, 1913, 12, 225–236.

228. KATSCH, G. and BORCHERS, E. Über physikalische Beeinflussung der Darmbewegungen. *Ztschr. f. exper. Path. u. Therap.* 1913, 12, 237–252

229. KEITH, A. Anatomical evidence as to the nature of the caecum and appendix. *J. Anat. & Physiol.*, 1903, 38, vii–xx.

230. KEITH, A. An account of six specimens of the great bowel removed by operation; with some observations on the motor mechanism of the colon. *Brit. J. Surg.*, 1915, 2, 576–599.

231. KEITH, A. The Cavendish Lecture on a new theory of the causation of enterostasis. *Lancet*, 1915, 2, 371–375.

232. KEITH, A. and JONES, F. W. A note on the development of the fundus of the human stomach. *J. Anat. & Physiol.*, 1902, 36, xxxiv–xxxviii.

233. KELLING, G. Studien zur Chirurgie des Magens. *Arch. f. klin. Chir.*, 1900, 62, 1–42, 288–338.

234. KELLING, G. Untersuchungen über die Spannungszustände der Bauchwand, der Magen- und der Darmwand. *Ztschr. f. Biol.*, 1903, 44, 161–258.

235. KIENBÖCK, R. Zur Röntgendiagnose der Colitis ulcerosa. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1913, 20, 231–239.

236. KIRSCHNER, M. and MANGOLD, E. Die motorische Funktion des Sphincter pylori und des Antrum pylori beim Hunde nach der queren Durchtrennung des Magens. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1911, 23, 446–494.

237. KIRSTEIN, A. Experimentelles zur Pathologie des Ileus. *Deutsch. med. Wchnschr.*, 1889, 15, 1000–1002.

238. KNOWLTON, F. P. and MOORE, A. R. Note on the reversal of reciprocal inhibition in the earthworm. *Am. J. Physiol.*, 1917, **44**, 490–491.

239. KÖLBING, P. Beiträge zur Magendarmchirurgie. *Beitr. z. klin. Chir.*, 1902, **33**, 518–534.

240. KÖLLIKER, A. Handbuch der Gewebelehre des Menschen. Leipzig, 1902, Ed. 6, Band 3.

241. KREHL, R. Über die Folgen der Vagusdurchschneidung. *Arch. f. Anat. u. Physiol.*, 1892, Physiol. Abth., suppl. Bd., 278–290.

242. KREIDL, A. und MÜLLER, A. Beiträge zur Physiologie des Verdauungstraktes: Mitt. I, II, III. *Arch. f. d. ges. Physiol.*, 1907, **116**, 159–185.

243. KRETSCHMER, H. L. The retrograde movement of ureteral calculi. *J. Am. M. Assn.*, 1918, **71**, 1355–1359.

244. KROGH, A. The number and distribution of capillaries in muscles, with calculations of the oxygen pressure head necessary for supplying the tissue. *J. Physiol.*, 1919, **52**, 409–415.

245. KUNTZ, A. The distribution of sympathetic neurones in the myenteric and submucous plexuses in the small intestine of the cat. *Anat. Record.*, 1918, **14**, 42.

246. KURODA, M. Observations of the effects of drugs on the ileo-colic sphincter. *J. Pharmacol & Exper. Therap.*, 1916, **9**, 187–195.

247. KUSSMAUL, A. Die peristaltische Unruhe des Magens, nebst Bemerkungen über Tiefstand und Erweiterung desselben, das Klatschgeräusch und Galle im Magen. *Samml. klin. Vortr.* (Volkmann), 1880, 1637–1674.

248. LANGLEY, J. N. On the question of commissural fibers between nerve cells having the same function and situated in the same sympathetic ganglion, and on the function of post-ganglionic nerve plexuses. *J. Physiol.*, 1904, **31**, 244–259.

249. LANGLEY, J. N. Trophic centre of the afferent fibres accompanying the sympathetic nerves. *J. Physiol.*, 1905, **33**, xvii–xviii.

250. LANGLEY, J. N. and MAGNUS, R. Some observations of the movements of the intestine before and after degenerative section of the mesenteric nerves. *J. Physiol.*, 1905, **33**, 34–51.

251. LANGMANN, G. A. On antiperistaltic movement. Jacobi Festschr., New York, 1900, p. 375.

252. LANSDOWN, R. G. P. and WILLIAMSON, G. S. The Etiology of appendicitis, gastric ulcer, and allied conditions. *Brit. J. Surg.*, 1914, **2**, 306–324.

253. LAPICQUE, M. et Mme. L. Durée des processus d'excitation pour differents muscles. *Compt. rend. hebd. d. Séances de l'Acad. des Sc.*, 1905, **140**, 801–804.

254. LAQUEUR, E. Die verschiedene Geschwindigkeit der Darmbewegungen bei verschiedenen Tieren. *Zentralbl. f. Physiol.*, 1914, **27**, 274–275.

255. LATARJET, A. et FORGEOT, E. Circulation artérielle de l'intestin grêle. *J. de l'anat. et physiol*, 1910, **46**, 483–510.

256. LEBON, H. and AUBOURG. Contractions reflexes du gros intestin par excitation de l'estomac. *Presse méd.* 1913, **21**, 566–567.

257. LEDDERHOSE. Ein Fall von Gastroenterostomie wegen Stenose des unteren Duodenum. *Arch. f. klin. Chir.*, 1899, **59**, 153–156.

258. LEE, F. S., GUENTHER, A. E. and MELENY, H. E. Some of the general physiological properties of diaphragm muscle as compared with certain other mammalian muscles. *Am. J. Physiol.*, 1916, **40**, 446–473.

259. LEGROS, et ONIMUS. Recherches experimentales sur les mouvements de l'intestin. *J. de l'anat. et. physiol.*, 1869, 37–66.

260. LENK, R. and EISLER, F. Experimentell-radiologische Studien zur Physiologie und Pathologie des Verdauungstraktes. *München. med. Wchnschr.*, 1913, **60**, 1031–1032.

261. LEVEN, G. et BARRET, G. Radioscopie gastrique. *Arch. d. mal. de l'appar. digest.*, 1907, **1**, 142–160.

262. LEWIS, F. T. The form of the stomach in human embryos with notes upon the nomenclature of the stomach. *Am. J. Anat.*, 1912, **13**, 477–503.

263. LEWIS, T. The mechanism and graphic registration of the heart beat. New York, 1920.

264. LEWIS, M. R. and LEWIS, W. H. The contraction of smooth muscle cells in tissue cultures. *Am. J. Physiol.*, 1917, **44**, 67–74.

265. LEWIS, T. and MATHISON, G. C. Auriculo-ventricular heart-block as a result of asphyxia. *Heart*, 1910, **2**, 47–53.

266. LILLIE, R. S. The conditions determining the rate of conduction in irritable tissues and especially in nerves. *Am. J. Physiol.*, 1914, **34**, 414–445.

267. LILLIE, R. S. The formation of structures resembling organic growths by means of electrolytic local action in metals and the general physiological significance and control of this type of action. *Biol. Bull.*, 1917, **33**, 135–186.

268. LILLIE, R. S. The nature of protoplasmic and nervous transmission. *J. Phys. Chem.*, 1920, **24**, 165–191.

269. LINTWAREW, S. J. Über die Rolle der Fette beim Übergang des Mageninhalts in den Darm. *Biochem. Centralbl.*, 1903, **1**, 96–97.

270. LOEB, J. Comparative physiology of the brain and comparative psychology. New York, 1900.

271. LOEB, J. The dynamics of living matter. New York, 1906.

272. LONDON, E. S. Zur Kenntnis des Verdauungs- und Resorptionsgesetze. I. Mitt: Methodische Angaben. *Ztschr. f. Phys. Chemie*, 1910, **65**, 189–192.

273. LONG, J. H. and FENGER, F. On the normal reaction of the intestinal tract. *J. Am. Chem. Soc.*, 1917, **39**, 1278–1286.

274. LÖWENTHAL, M. Beiträge zur Diagnostik und Therapie der Magenkrankheiten. *Berl. klin. Wchnschr.*, 1892, **29**, 1188–1190.

275. LUCAS, D. R. Studies of the peristalsis of the ureter of dogs by the graphic method. *Am. J. Physiol.*, 1906, **17**, 392–407.

276. LUCIANI, L. Human physiology. London, 1913, **2**, 232–236.

277. Luckhardt, A. B., Phillips, H. T. and Carlson, A. J. Contributions to the physiology of the stomach. LI. The control of the pylorus. *Am. J. Physiol.*, 1919, **50**, 57–66.

278. Lüderitz, C. Experimentelle Untersuchungen über die Entstehung der Darmperistaltik. *Virchow's Arch.*, 1889, **118**, 19–36.

279. Lüderitz, C. Experimentelle Untersuchungen über die Entstehung der Darmperistaltik. *Virchow's Arch.*, 1890, **122**, 1–28.

280. Lüderitz, C. Das motorische Verhalten des Magens bei Reizung seiner ausseren Fläche. *Arch. f. d. ges. Physiol.*, 1891, **49**, 158–174.

281. Lüdin, M. Der Einfluss von Zwischenmahlzeiten bei der röntgenologischen Prüfung der Magenmotilität. *Deutsche med. Wchnschr.*, 1913, **39**, 1239–1241.

282. Lund, E. J. Control of morphological polarity by means of the electric current. *Proc. Amer. Soc. Zool.* Anat. Record, 1921, **20**, 188.

283. Luschka, H. Die organische Musculatur innerhalb verschiedener Falten des menschlichen Bauchfelles. *Arch. f. Anat. u. Physiol.*, 1862, 202–209.

284. Lyman, H. The receptive relaxation of the colon. *Am. J. Physiol.*, 1913, **32**, 61–64.

285. Macewen, W. The function of the caecum and appendix. *Lancet*, 1904, **2**, 995–1000.

286. Mackenzie, W. C. The spleen in monotremes and marsupials. *J. Anat.*, 1916, **51**, 1–18.

287. Mackenzie, W. C. Further studies on the peritoneum and intestinal tract in monotremes and marsupials. *J. Anat. & Physiol.*, 1917, **51**, 278–292.

288. Macarthur, C. G. and Jones, O. C. Some factors influencing the respiration of ground nervous tissue. *J. Biol. Chem.*, 1917, **32**, 259–274.

289. Magnus, R. I. Mitteil: Versuche am überlebenden Dünndarm von Säugethieren. *Arch. f. d. ges. Physiol.*, 1904, **102**, 123–151.

290. Magnus, R. II. Mitteil: Die Beziehungen des Darmnervensystems zur automatischen Darmbewegung. *Arch. f. d. ges. Physiol.*, 1904, **102**, 349–363.

291. Magnus, R. III. Mitteil: Die Erregungsleitung. *Arch. f. d. ges. Physiol.*, 1904, **103**, 515–524.

292. Magnus, R. IV. Mitteil: Rhythmizität und refraktäre Periode. *Arch. f. d. ges. Physiol.*, 1904, **103**, 525–540.

293. Magnus, R. V. Mitteil: Wirkungsweise und Angriffspunkt einiger Gifte am Katzendarm. *Arch. f. d. ges. Physiol.*, 1905, **108**, 1–71.

294. Magnus, R. VI. Mitteil: Versuche am überlebenden Dünndarm von Säugetieren. *Arch. f. d. ges. Physiol.*, 1906, **111**, 152–160.

295. Magnus, R. Die Bewegungen des Verdauungskanals. *Ergebn. d. Physiol.*, 1908, **7**, 27–64.

296. Magnus, R. Die Bewegungen des Verdauungsrohres. Tigerstedt's Handbuch der physiologischen Methodik. Leipzig, 1911, II, zw. Abth., 99–149.

297. MALEYX, H. Contribution a l'étude des hemorrhagies et des perforations intestinales à distance au cours des obstructions terminales du gros intestin. Paris, *Thèse*, 1912.

298. MALL, F. A study of the intestinal contractions. *Johns Hopkins Hosp. Rep.*, 1896, **1**, 37–75.

299. MALL, F. Reversal of the intestine, *Johns Hopkins Hosp. Rep.*, 1896, **1**, 93–110.

300. MARBAIX, O. Le passage pylorique. *La Cellule*, 1898, **14**, 249–332.

301. MATHEWS, A. P. Electrical polarity in the hydroids. *Am. J. Physiol.*, 1902, **8**, 294–299.

302. MAY, W. P. The innervation of the sphincters and musculature of the stomach. *J. Physiol.*, 1904, **31**, 260–271.

303. MAYER, A. G. Nerve conduction, and other reactions in cassiopea. *Am. J. Physiol.*, 1916, **39**, 375–393.

304. MAYER, S. Erbrechen. Hermann's Handbuch der Physiologie, 1883, **5**, 444.

305. MAYO, W. J. Gastric ulcer. *J. Am. M. Assn.*, 1915, **65**, 1069–1073.

306. MCCLENDON, J. F. New hydrogen electrodes and rapid methods of determining hydrogen ion concentrations. *Am. J. Physiol.*, 1915, **38**, 180–185.

307. MCCLENDON, J. F. Acidity curves in the stomachs and duodenums of adults and infants, plotted with the aid of improved methods of measuring the hydrogen ion concentration. *Am. J. Physiol.*, 1915, **38**, 191–199.

308. MCCLENDON, J. F., SHEDLOV, A. and KARPMAN, B. The hydrogen ion concentration of the contents of the small intestine. *J. Biol. Chem.*, 1918, **34**, 1–3.

309. MCCLENDON, J. F., MYERS, F. J., CULLIGAN, L. C. and GYDESEN, C. S. Factors influencing the hydrogen ion concentration of the ileum. *J. Biol. Chem.*, 1919, **38**, 535–538.

310. MCCLENDON, J. F., BISSELL, F. S., LOWE, E. R. and MEYER, P. F. Hydrogen ion concentration of the contents of the small intestine. *J. Am. M. Assn.*, 1920, **75**, 1638–1641.

311. MCCLURE, C. W., REYNOLDS, L., and SCHWARTZ, C. O. On the behavior of the pyloric sphincter in normal man. *Arch. Int. Med.*, 1920, **26**, 410–423.

312. MCCLURE, R. D., and DERGE, H. F. A study of reversal of the intestine. *Johns Hopkins Hosp. Bull.*, 1907, **18**, 472–474.

313. MCGILL, C. The structure of smooth muscle in the resting and in the contracted condition. *Am. J. Anat.*, 1909, **9**, 493–545.

314. MCGUIGAN, H. and BECHT, F. C. The site of the action of strychnine, *J. Pharmacol. & Exper. Therap.*, 1914, **5**, 469–478.

315. MCGUIGAN, H., KEETON, R. W. and SLOAN, L. H. The segmental action of strychnine. *J. Pharmacol & Exper. Therap.*, 1916, **8**, 143–154.

316. Meek, W. J. The regeneration of nerve and muscle in the small intestine, *Am. J. Physiol.*, 1910, 25, 367–384.

317. Meltzer, S. J. Direct and indirect faradization of the digestive canal. *N. York M. J.*, 1895, 61, 746–750.

318. Mering, J. von. Über die Function des Magens. *Verhandl. d. deutsch. Kong. f. innere Med.*, 1893, 471–487.

319. Merkel, F. Handbuch der Topographischen Anatomie. Braunschweig, 1899, II, 570–578.

320. Miller, F. R. On gastric sensation. *J. Physiol.*, 1910, 41, 409–415.

321. Mines, G. R. On the spontaneous movements of amphibian skeletal muscle in saline solutions, etc. *J. Physiol.*, 1908, 37, 408–444.

322. Mitchell, P. C. On the intestinal tract of mammals. *Tr. Zoöl. Soc.*, London, 1905, 17, 437–536.

323. Monks, G. H. Intestinal localization. *Tr. Am. Surg. Assn.*, 1903, 21, 405–424.

324. Monks, G. H. Studies in the surgical anatomy of the small intestine and its mesentery. *Ann. Surg.*, 1905, 42, 543–569.

325. Moore, A. R. Reversal of reaction by means of strychnine in planarians and starfish. *J. Gen. Physiol.*, 1918, 1, 97–100.

326. Morishima, K. and Fujitani, J. Zur Untersuchungsmethode der spontanen Bewegung des Froschmagens. *Arch. f. exper. Path.*, Suppl. B, 1908, p. 407–414.

327. Moritz, Studien über die motorische Thätigkeit des Magens. II. Mitteilung: Über die Beeinflussung der Geschwindigkeit der Magenentleerung durch die Beschaffenheit der Ingesta. *Ztschr. f. Biol.*, 1901, 42, 565–611.

328. Morse, W. E. The relation of acid to gastric discharge and duodenal regurgitation in the dog. *Am. J. Physiol.*, 1916, 41, 439–448.

329. Moynihan, B. G. A. A case of gastro-jejunostomy for complete rupture of the intestine at the duodenojejunal flexure. *Brit. M. J.*, 1901, 1, 1136.

330. Moynihan, B. G. A. Abdominal operations. Philadelphia. 1906.

331. Mühsam, R. Experimentelles zur Frage der Antiperistaltik. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1900, 6, 451–461.

333. Müller, A. Beiträge zur Kenntnis von Schutzeinrichtungen des Darmtraktes gegen spitze Fremdkörper. *Arch. f. d. ges. Physiol.*, 1904, 102, 206–216.

334. Müller, A. und Hesky O. Über die Folgeerscheinungen nach operativer Entfernung der Darmmuskulatur, insbesondere am Dickdarm und Rectum. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1911, 22, 104–110.

335. Müller, A. und Kondo, K. Über die Folgeerscheinungen nach operativer Entfernung der Längsmuskulatur des Darmes. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1912, 24, 512–515.

336. Müller, L. R. Die Darminnervation. *Deutsches Arch. f. klin. Med.*, 1911, 105, 1–43.

337. Müller-Hettlingen, J. Über galvanische Erscheinungen an keimenden Samen. *Arch. f. d. ges. Physiol.*, 1883, **31**, 193–214.

338. Myers, F. J. and McClendon, J. F. Note on the hydrogen ion concentration of the human duodenum. *J. Biol. Chem.*, 1920, **41**, 187–190.

339. Neilson, C. H. and Lipsitz, S. T. The effect of various procedures on the passage of liquids from the stomach. *J. Am. M. Assn.*, 1915, **64**, 1052–1055.

340. Neuburger, M. History of Medicine. Translated by Playfair. London, 1910, **1**, p. 29.

341. Neumann, K. O. The afferent fibres of the abdominal vagus in the rabbit and cat. *J. Physiol.*, 1914, **49**, 34–37.

342. Niwa, S. The effect of cocaine hydrochloride on the CO_2 production of the mixed nerve fiber. *J. of Pharmacol & Exper. Therap.*, 1919, **12**, 323–342.

343. Nothnagel, C. W. H. Beiträge zur Physiologie und Pathologie des Darmes. Berlin, 1884.

344. Okinczyc, J. Chirurgie du gros intestin. *Presse Méd.*, 1919, **27**, 581–584.

345. Openchowski, T. Über die nervösen Vorrichtungen des Magens. *Zentralbl. f. Physiol.*, 1889, **3**, 1–10.

346. Oppel, A. Lehrbuch der vergleichenden mikroskopischen Anatomie der Wirbeltiere. Erster Teil–Der Magen. Jena, 1896.

347. Ostwald, W. Periodische Erscheinungen bei der Auflösung des Chroms in Säuren. *Ztschr. f. Phys. Chemie*, 1900, **35**, 33–76, 204–256.

348. Parker, G. H. Some underlying principles in the structure of the nervous system. *Science*, 1918, **47**, 151–162.

349. Parker, G. H. The rate of transmission in the nerve net of the coelenterates. *J. Gen. Physiol.*, 1918, **1**, 231–236.

350. Parker, G. H. The elementary nervous system. Philadelphia, 1919.

351. Parnas, T. Energetick glatter Muskeln. *Arch. f. d. ges. Physiol.*, 1910, **134**, 441–495.

352. Paterson, H. J. Appendicular gastralgia or the appendix as a cause of gastric symptoms. *Proc. Roy. Soc. Med.*, 1910, **3**, Surg. Sect., 187–208.

353. Paukul, E. Die Zuckungsformen von Kaninchenmuskeln verschiedener Farbe und Structur. *Arch. f. Anat. u. Physiol.*, 1904, Physiol. Abth., 100–120.

354. Pavloff, J. P. Die physiologische Chirurgie des Verdauungskanals. *Ergebn. d. Physiol.*, 1902, **1**, 246–284.

355. Pavloff, J. P. The work of the digestive glands. Transl. by Thompson W. 2nd Edit., London, 1910.

356. Pavloff, J. P. Die operative Methodik des Studiums der Verdauungsdrüsen. Tigerstedt's Handbuch der Physiologischen Methodik. Leipzig, 1911, II, zw. Abth., 150–188.

357. Pearce, R. G. A history of the physiology of digestion. *Cleveland M. J.*, 1914, **13**, 343–350.

358. PENFIELD, W. G. Contraction waves in the normal and hydronephrotic ureter; an experimental study. *Am. J. M. Sc.*, 1920, **160**, 36–46.

359. PEYER, A. Über Magenaffektionen bei männlichen Genitalleiden. *Samml. klin. Vortr.* (Volkmann), 1890, 4, 3169–3204.

360. POENSGEN, E. Die motorischen Verrichtungen des menschlichen Magens und ihre Störungen mit Ausschluss der Lehre vom Erbrechen. Strassburg, 1882.

361. POHL, J. Über Darmbewegungen und ihre Beeinflussung durch Gifte. *Arch. f. exper. Path. u. Pharmakol.*, 1894, **34**, 87–104.

362. POMPILIAN. Sur la contraction musculaire de l'Escargot. *Compt. rend. Soc. de. biol.*, 1899, **51**, 489–490.

363. PORTER, E. L. Variations in irritability of the reflex arc. II. Variations under strychnine. *Am. J. Physiol.*, 1915, **36**, 171–182.

364. PRESSLER, K. Beobachtungen und Versuche über den normalen und inversen Situs viscerum et cordis bei Anurenlarven. *Arch. f. Entwcklngs-mechn. d. Organ.*, 1911, 32, 1–35.

365. PRUTZ, W. and ELLINGER, A. Über die Folgen der Darmgegenschaltung. Zugleich ein Beitrag zur Lehre von der Indicanurie. *Arch. f. klin. Chir.*, 1902, **67**, 964–995.

366. PRUTZ, W. and ELLINGER, A. Über die Folgen der Darmgegenschaltung. II. Mitteil: Zugleich ein Beitrag zur Frage der sogenannten Antiperistaltik.*Arch. f. klin. Chir.*, 1904, 72, 415–448.

367. QUIMBY, A. J. Roentgen interpretation of intestinal conditions. *Am. J. Roentgenol.*, 1914, **1**, 399–403.

368. QUIROT, M. La forme gastrique de l'occlusion intestinale chronique. Paris, Thése, 1909.

369. RANVIER, L. A. Leçons d'anatomie generale faites au College de France. Paris, 1880, 433.

370. RAASCHE, A. Über eigentümliche Veränderungen der Herztätigkeit unter dem Einfluss von Chloroform. *Ztschr. f. Biol.*, 1911, 55, 469–490.

371. REACH, F. Über rückläufige Fortbewegung von Darminhalt. *Prag. med. Wchnschr.*, 1902, 27, 549–550.

372. REHFUSS, M. E., Bergeim, O. and HAWK, P. B. Gastro-intestinal studies. I. The question of the residuum found in the empty stomach. *J. Am. M. Assn.*, 1914, **63**, 11–13.

373. REICHEL, P. Zur Pathologie des Ileus und Pseudoileus. *Deutsch. Ztschr. f. Chir.*, 1893, 35, 495–553.

374. REICHMANN, M. Über sogenannte Dyspepsia acida. *Berl. klin. Wchnschr.*, 1884, **21**, 768–771.

375. ROITH, O. Über die Peristaltik und Antiperistaltik des menschlichen Dickdarmes. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1913, 25, 203–210.

376. ROLLESTON, H. D. and JEX-BLAKE, A. J. On the occurrence of vomiting during rectal alimentation. *Brit. M. J.*, 1903, 2, 68–69.

377. ROSENBERG, S. Die physiologischen Folgen der Gastroenterostomie. *Arch. f. d. ges. Physiol.*, 1898, **73**, 403–421.

378. ROST, F. Die anatomischen Grundlagen der Dickdarmperistaltik. *Arch. f. klin. Chir.*, 1912, **98**, 984–992.

379. RUBASCHOU, S. Beitrag zur Lehre über die Folgen der Vagotomie. *Internat. Beitr. z. Path. u. Therap. d. Ernährungsstör.*, 1912, **3**, 462–484.

380. RUTHERFORD, A. H. The ileocecal valve. New York, 1914.

381. SABBATANI, L. Nuovo metodo per osservare le intestina. *Archiv. di fisiol.*, 1909, **6**, 265–268.

382. SANDERS, EZN. H. Methode tot onderzoek der peristaltische Bewegingen van het darmkanaal, enz. Voorloop. mededeel. Abstract in *Centralbl. f. d. med., Wissensch.*, 1871, 479.

383. SATANI, Y. Experimental studies of the ureter. *Am. J. Physiol.*, 1919, **49**, 474–495.

384. SCHAFER, E. A. Text-book of microscopic anatomy. London, 1912, 2, 536–552.

385. SCHIEFFERDECKER, P. Untersuchung einer Anzahl von Kaumuskeln des Menschen und einiger Säugetiere in bezug auf ihren Bau und ihre Kernverhältnisse nebst einer Korrektur meiner Herzarbeit. *Arch. f. d. ges. Physiol.*, 1919, **173**, 265–384.

386. SCHILLBACH, E. Studien über den Einfluss der Elektricität auf den Darm. *Virchow's Arch.*, 1887, **109**, 278–288.

387. SCHILLING, F. Wasser im Munde, Wasserspeien, Wasserkolik. *Zentralbl. f. inn. Med.*, 1915, **36**, 501–516.

388. SCHLOFFER, H. Über Ileus bei Hysterie. *Beitr. z. klin. Chir.*, 1899, **24** 392–417.

389. SCHMIDT, J. E. Ein Beitrag zur Frage der Magensensibilität. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1909, **19**, 278–281.

390. SCHULTZ, P. Die glatte Musculatur der Wirbelthiere (mit Ausnahme der Fische). *Arch. f. Anat. u. Physiol.*, 1895, Physiol. Abth., p. 517–550.

391. SCHULTZ, P. Zur Physiologie der längsgestreiften (glatten) Muskeln der Wirbelthiere. IV. Beitrag. *Arch. f. Anat. u. Physiol.*, 1903, Physiol. Abth., Suppl., 1–148.

392. SCHUR, H. Über Hyperaciditätschmerzen und Ulcus ventriculi. *Med. Klinik*, 1911, **7**, 919–921.

393. SCHÜTZ, E. Über Hyperacidität. *Wien. med. Wchnschr.*, 1906, **56**, 2241–2249.

394. SCHWARZ, G. Über hypokinetische und dyskinetische Formen der Obstipation. *München. Med. Wchnschr.*, 1912, **59**, 2153–2155.

395. SEGALE, M. The temperature of acutely inflamed peripheral tissue. *J. Exper. M.*, 1919, **29**, 235–249.

396. SENN, N. Intestinal surgery. Chicago, 1889.

397. SHERRINGTON, C. S. The integrative action of the nervous system. New Haven, 1911.

398. SHERRINGTON, C. S. Postural activity of muscle and nerve. *Brain*, 1915, 38, 191–234.

399. SHIMODAIRA, Y. Experimentelle Untersuchungen über die Entstehung von sogenannten Dehnungsgeschwüren des Darmes. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1911, 22, 229–310.

400. SICK, K., and TEDESKO, F. Studien über Magenbewegung mit besonderer Berüchsichtigung der Ausdehnungsfähigkeit des Hauptmagens (Fundus), *Deutsch. Archiv. f. klin. Med.*, 1908, 92, 416–451.

401. SINGER, G. and HOLZKNECHT, G. Über objektive Befunde bei der spastischen Obstipation. *München. med. Wchnschr.*, 1911, 58, 2537–2539.

402. SLOWTZOFF, B. Appareil pour l'étude de l'activité de l'intestin en dehors de l'organisme. *Compt. rend. Soc. biol.*, 1916, 79, 84–85.

403. SMITH, C. H. and LEWALD. The influence of posture on digestion in infancy. *Am. J. Dis. Child.*, 1915, 9, 261–282.

404. SMITHIES, F. What facts of diagnostic or prognostic value can be determined from test-meal examination of patients with gastric symptoms? *Am. J. M. Sc.*, 1915, 149, 183–193.

405. SOKOLOFF, O. and LUCHSINGER, B. Zur Physiologie der Ureteren. *Archiv. f. d. ges. Physiol.*, 1881, 26, 464–469.

406. SPADOLINI, I. Le azioni antagonistiche nei sistemi autonomi. *Arch. di fisiol.*, 1916, 15, 1–168.

407. SPADOLINI, I. Contributo allo studio dell' innervazione estrinseca dello stomaco e dell' intestino tenue. *Arch. di fisiol.*, 1917, 15, 229–243.

408. SPENCER, W. H., MEYER, G. P., REHFUSS, M. E. and HAWK, P. B. Gastro-intestinal studies. XII. Direct evidence of duodenal regurgitation and its influence upon the chemistry and function of the normal human stomach. *Am. J. Physiol.*, 1916, 39, 459–479.

409. STEELE, J. D. The relation of excessive gastric acidity to gastric symptoms. *J. Am. M. Assn.*, 1906, 47, 496–500.

410. STEWART, G. D. and BARBER, W. H. Segmental resection for gastric ulcer. *Ann. Surg.*, 1916, 64, 527–536.

411. STIERLIN. Die radiologische Diagnostik der Ileo-coecaltuberkulose und anderer ulcerativer und indurierender Dickdarmprozesse. *Zentralbl. f. Röntgenstr.*, 1911, 2, 254.

412. STILES, P. G. On the rhythmic activity of the oesophagus and the influence upon it of various media. *Am. J. Physiol.*, 1901, 5, 338–357.

413. STOCKTON, C. G. Diseases of the stomach and their relation to other diseases. New York, 1914.

414. STRAUB, W. Zur Muskelphysiologie des Regenwurms. *Arch. f. d. ges. Physiol.*, 1900, 79, 379–399.

415. Straub, W. Zur Physiologie des Aplysienherzens. *Arch. f. d. ges. Physiol.*, 1901, 86, 504–532.

416. Straub, W. Fortgesetzte Studien am Aplysienherzen (Dynamik, Kreislauf und dessen Innervation) nebst Bemerkungen zur vergleichenden Muskelphysiologie. *Arch. f. d. ges. Physiol.*, 1904, 103, 429–449.

417. Surmont, H. and Dubus, A. De l' excitation à distance de la motricité colique. *Arch. de mal. de l'appar. digest.*, 1912, 6, 181–195.

418. Swiezynski, J. Nachprüfung der Grütznerschen Versuche über das Schicksal von Rectalinjectionen an Menchen und Thieren. *Deutsche med. Wchnschr.*, 1895, 21, 514–516.

419. Symes, W. L. Observations on anaesthesia by phenylethylmalonyl urea. *J. Physiol.*, 1915, 49, 126–132.

420. Tabora, von. Über motorische Magenreflexe. *Zentralbl. f. Röntgenstrablen*, 1912, 2, 247.

421. Takahashi, M. Die Abhängigkeit der Magenentleerung vom Allgemeinzustand des Nervensystems. *Arch. f. d. ges. Physiol.*, 1914, 159, 389–392.

422. Tashiro, S. A chemical sign of life. Chicago, 1917.

423. Taylor, A. E. Digestion and metabolism. Philadelphia, 1912.

424. Taylor, F. B. and Alvarez, W. C. VIII. The effect of temperature on the rhythm of excised segments from different parts of the intestine. *Am. J. Physiol.*, 1917, 44, 344–352.

425. Thomsen, E. Über die Einwirking des Zuckers auf die Verdauung. *Ztschr. f. Phys. Chemie*, 1913, 84, 425–436.

426. Tobler, L. Über die Eiweissverdauung im Magen. *Ztschr. f. Phys. Chemie*, 1905, 45, 185–215.

427. Todd, T. W. The clinical anatomy of the gastro-intestinal tract. Manchester, 1915.

428. Toldt, C. Die Formbildung des menschlichen Blinddarmes und die Valvula coli. *Sitzungsb. d. Wien. Akad. d. Wissensch.*, Math.–Naturw. Cl., 1894, 103, iii, 41–71.

429. Tourneux, F. et Hermann, G. Intestin (histologie). *Dict. Encycloped. d. Sc. Méd.*, 1889, 4 Serie, 16, 241.

430. Trendelenburg, P. Eine neue Methode zur Registrierung der Darmtätigkeit. *Ztschr. f. Biol.*, 1913, 61, 67–72.

431. Trendelenburg, P. Physiologische und pharmakologische Versuche über die Peristaltik des Dünndarms. *Arch. f. exper. Path. u. Pharmakol.*, 1917, 81, 53–129.

432. Trendelenburg, P. Physiologische und pharmakologische Versuche über die Peristaltik des Dünndarms. *Deutsche med. Wchnschr.*, 1917, 43, 1225–1227.

433. Treves, F. The value of abdominal exploration as a medical measure. *Lancet*, 1898, 1, 643–644.

434. Treves, F. Intestinal obstruction. New York, 1902.

435. UEXKÜLL, J. von. Die ersten Ursachen des Rhythmus in der Tierreiche. *Ergebn. d. Physiol.*, 1904, 3, part 2, 1–11.

436. UFFENHEIMER, A. Weitere Studien über die Durchlässigkeit des Magendarmkanales für Bakterien. *Deutsche med. Wchnschr.*, 1906, 32, 1851–1854.

437. VELLA, L. Nuova metodo per avere succo enterico puro e stabilirne le proprieta fisiologiche. *Bull. d. sc. med., Bologna*, 1881, 6 s., 7, 441–443.

438. VERSON, E. Stricker's Manual of Histology. American Translation by Buck. New York, 1872.

439. VERZAR, F. Über glatte Muskelzellen mit myogenem Rhythmus. *Arch. f. d. ges. Physiol.*, 1914, 158, 419–420.

440. WATERSTON, D. The effects of formalin hardening and the persistence of irritability in the muscular coats of the intestine. *J. Anat. & Physiol.*, 1910, 45, 16–19.

441. WEBER, F. P. Faecal vomiting and reversed peristalsis in functional nervous (cerebral) disease: A summary of cases and conclusions. *Brain*, 1904, 27, 170–198.

442. WEGELE, C., GROSS, M. H. and HELD, I. W. Therapeutics of the gastro-intestinal tract. New York, 1913.

443. WEIL, A. Über dem Einfluss elektrischer Reize auf Magenperistaltik und—Sekretion beim Menschen. *Deutsche Archiv. f. klin. Med.*, 1913, 109, 486–497.

444. WHEELON, H. and THOMAS. Observations on the motility of the antrum and the relation of the rhythmic activity of the pyloric sphincter to that of the antrum. *J. Lab. & Clin. M.*, 1920, 6, 124–143.

445. WHITE, F. W. Effect of stimuli from the lower bowel on the rate of emptying the stomach. *Am. J. M. Sc.*, 1918, 156, 184–189.

446. WEIDEMANN, H. Experimentelle Untersuchungen zur Lehre der Verdauung und Resorption verschiedener Nahrungsprodukte bei anormalem Gallenzufluss in den Verdauungsapparat. *Beitr. z. klin. Chir.*, 1914, 89, 594–598.

447. WILLIAMS, H. B. and JAMES, H. Reversal of the cardiac mechanism. *Heart*, 1914, 5, 109–115.

448. WILSON, F. N. The production of atrioventricular rhythm in man after the administration of atropin. *Arch. Int. Med.*, 1915, 16, 989–1007.

449. WISLOCKI, G. B. and O'CONNOR, V. J. Experimental observations upon the ureters, with especial reference to peristalsis and antiperistalsis. *Johns Hopkins Hosp. Bull.*, 1920, 31, 197–202.

450. WOLFF, W. Die Bewegungen des Duodenums, nebst Bemerkungen über einzelne Bewegungsformen des Dünndarms überhaupt. Inaug. Dissertation. Giessen, 1902.

451. WOODWORTH, R. S. Studies in the contraction of smooth muscle. *Am. J. Physiol.*, 1900, 3, 26–44.

452. WORDEN, C. B., SAILER, J., PANCOAST, H. K., and DAVIS, G. G. A clinical study of gastroptosis, with special reference to the value of the bismuth skiagraph shadow in determining the topography of the gastro-intestinal tract. *Univ. Penn. M. Bull.*, 1906, **19**, 122–141.

453. YANASE, J. Beiträge zur Physiologie der peristaltischen Bewegungen des embryonalen Darmes. *Arch. f. d. ges. Physiol.*, 1907, **117**, 345–383.

454. ZILWA, A. E. de. Some contributions to the physiology of unstriated muscle. *J. Physiol.*, 1901, 27, 200–223.

455. ZIMMERMANN, R. Experimentelle Untersuchungen über die Empfindungen in der Schlundröhre und im Magen, in der Harnröhre und in der Blase und im Enddarm. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1909, 20, 445–457.

456. ZONDEK, B. Über Dickdarmperistaltik. Beobachtungen am experimentellen Bauchfenster. *Arch. f. Verdauungskr.*, 1920, 27, 18–23.

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